

WO2002064591

Title:
No title available

Abstract:

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064591 A2

(51) International Patent Classification⁷: **C07D 471/04**,
A61K 31/437, A61P 9/00, 15/10 // (C07D 471/04, 211:00,
209:00)

Maison Caloni, 1153 Route de Saleve, F-74560 Monnetier
Mornex (FR).

(21) International Application Number: PCT/US02/00017

(74) Agent: **NAPOLI, James, J.**; Marshall, Gerstein & Borun,
6300 Sears Tower, 233 South Wacker Drive, Chicago, IL
60606 (US).

(22) International Filing Date: 3 January 2002 (03.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/268,154 12 February 2001 (12.02.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*): **LILLY
ICOS LLC** [US/US]; 1209 Orange Street, Wilmington, DE
19801 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(72) Inventors; and

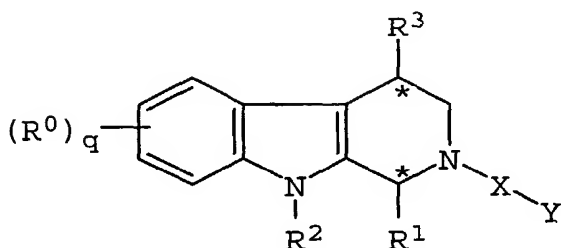
(75) Inventors/Applicants (*for US only*): **SAWYER, Jason,
Scott** [US/US]; 5718 North Winthrop Avenue, Indianapo-
lis, IN 46200 (US). **ORME, Mark, W.** [US/US]; 4235
Francis Avenue #203, Seattle, WA 98103 (US). **BROWN,
Raymond, F.** [US/US]; 10518 Greenway Drive, Fish-
ers, IN 46038 (US). **DAUGAN, Alain, Claude-Marie**
[FR/FR]; Centre de Recherche Glaxo Smith Kline
Courtaboeuf, ZA de Courtaboeuf, 25, avenue de Quebec,
F-91940 Les Ulis (FR). **BOMBRUN, Agnes** [FR/FR];

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CHEMICAL COMPOUNDS



(57) Abstract: Compounds of the general structural formula and use of the compounds and salts and solvates thereof, as therapeutic agents.

WO 02/064591 A2

- 1 -

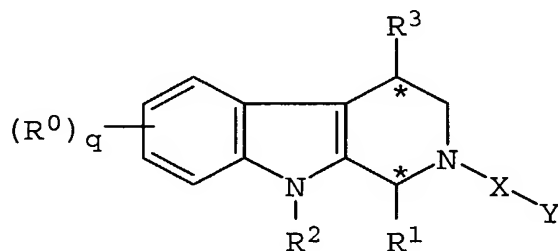
CHEMICAL COMPOUNDS

FIELD AND BACKGROUND OF THE INVENTION

5 This invention relates to a series of compounds, to methods of preparing the compounds, to pharmaceutical compositions containing the compounds, and to their use as therapeutic agents. In particular, the invention relates to compounds that
10 are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas wherein such inhibition is considered beneficial, including
15 the treatment of cardiovascular disorders and erectile dysfunction.

SUMMARY OF THE INVENTION

20 The present invention provides compounds of formula (I)

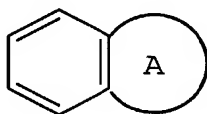


(I)

- 2 -

wherein R^0 , independently, is selected from the group consisting of halo, C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkylQ, $C(=O)R^a$, $OC(=O)R^a$, $C(=O)OR^a$, C_{1-4} alkylene NR^aR^b , C_{1-4} alkyleneHet, C_{1-4} alkylene $C(=O)OR^a$, $C(=O)NR^aSO_2R^c$, $C(=O)C_{1-4}$ alkyleneHet, $C(=O)NR^aR^b$, $C(=O)NR^aR^c$, $C(=O)NR^aC_{1-4}$ alkylene OR^b , $C(=O)NR^aC_{1-4}$ alkyleneHet, OR^a , OC_{1-4} alkylene $C(=O)OR^a$, OC_{1-4} alkylene NR^aR^b , OC_{1-4} alkyleneHet, OC_{1-4} alkylene OR^a , OC_{1-4} alkylene $NR^aC(=O)OR^b$, NR^aR^b , NR^aC_{1-4} alkylene NR^aR^b , $NR^aC(=O)R^b$, $NR^aC(=O)NR^aR^b$, $N(SO_2C_{1-4}alkyl)_2$, $NR^a(SO_2C_{1-4}alkyl)$, nitro, trifluoromethyl, trifluoromethoxy, cyano, $SO_2NR^aR^b$, SO_2R^a , SOR^a , SR^a , and OSO_2CF_3 ;

R^1 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, an optionally substituted C_{3-8} cycloalkyl ring, an optionally substituted C_{3-8} heterocycloalkyl ring, an optionally substituted bicyclic ring

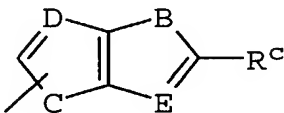


wherein the fused ring A is a 5- or 6-membered ring, saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one to three heteroatoms selected from oxygen, sulfur, and nitrogen, hydrogen, C_{1-6} alkyl, aryl C_{1-3} alkyl, C_{1-3} alkylenearyl, halo C_{1-6} alkyl, C_{1-4} alkylene $C(=O)OR^a$, C_{1-4} alkylene $C(=O)NR^aR^b$, C_{3-8} cycloalkenyl, C_{3-8} hetero-

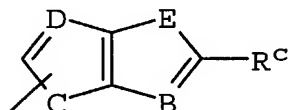
- 3 -

cycloalkenyl, C_{1-4} alkyleneHet, C_{1-4} alkyleneQR^a, C_{2-6} -
alkenyleneQR^a, C_{1-4} alkyleneQC₁₋₄alkyleneQR^a,

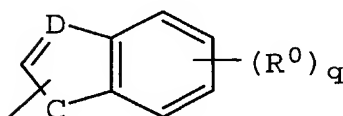
5



10



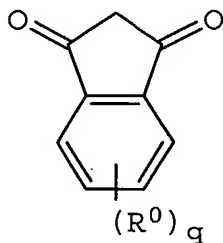
15



20

and a spiro substituent having a structure

25



30

- 4 -

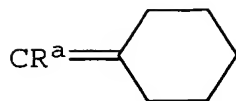
R^2 is selected from the group consisting of
 hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heterocyclo-
 alkyl, C_{2-6} alkenyl, C_{1-3} alkylenearyl, aryl C_{1-3} alkyl,
 heteroaryl C_{1-3} alkyl, aryl, heteroaryl, $C(=O)R^a$, $C(=O)-$
 5 NR^aR^b , $C(=O)NR^aR^c$, $C(=S)NR^aR^b$, $C(=S)NR^aR^c$, SO_2R^a ,
 $SO_2NR^aR^b$, $S(=O)R^a$, $S(=O)NR^aR^b$, $C(=O)NR^aC_{1-4}$ alkyleneOR^a,
 $C(=O)NR^aC_{1-4}$ alkyleneHet, $C(=O)C_{1-4}$ alkylenearyl, $C(=O)-$
 C_{1-4} alkyleneheteroaryl, C_{1-4} alkylenearyl substituted
 with one or more of $SO_2NR^aR^b$, NR^aR^b , NR^aR^c , $C(=O)OR^a$,
 10 $NR^aSO_2CF_3$, CN, NO_2 , $C(=O)R^a$, OR^a , C_{1-4} alkylene NR^aR^b , and
 OC_{1-4} alkylene NR^aR^b , C_{1-4} alkyleneheteroaryl, C_{1-4} alkylene-
 Het, C_{1-4} alkylene $C(=O)C_{1-4}$ alkylenearyl, C_{1-4} alkylene-
 $C(=O)C_{1-4}$ alkyleneheteroaryl, C_{1-4} alkylene $C(=O)Het$,
 C_{1-4} alkylene $C(=O)NR^aR^b$, C_{1-4} alkyleneOR^a, C_{1-4} alkylene-
 15 $NR^aC(=O)R^a$, C_{1-4} alkylene OC_{1-4} alkyleneOR^a, C_{1-4} alkylene-
 NR^aR^b , C_{1-4} alkylene $C(=O)OR^a$, and C_{1-4} alkylene OC_{1-4} alkyl-
 ene $C(=O)OR^a$;

R^3 is selected from the group consisting of
 hydrogen, C_{1-6} alkyl, aryl, heteroaryl, aryl C_{1-3} alkyl,
 20 C_{1-3} alkylenearyl, C_{1-3} alkyleneHet, C_{3-8} cycloalkyl, and
 C_{3-8} heterocycloalkyl;

X is selected from the group consisting of
 $C(=O)$, $C(=O)C\equiv C$, $C(=O)C(R^a)=C(R^a)$, $C(=S)$, SO, SO_2 ,
 $SO_2C(R^a)=CR^a$, CR^aR^b , $CR^a=CR^a$, $C(=O)NR^a$, and $C(=N-OR^a)$;

Y is selected from the group consisting of
 $(CH_2)_nC(=O)R^c$, $(CH_2)_nC(=O)OR^c$, $(CH_2)_n$ aryl, $N(R^b)(CH_2)_nR^c$,
 $O(CH_2)_nR^c$, $N(R^b)C(=O)R^c$, $C(R^a)=NR^c$, $C(=O)N(R^a)(R^c)$,
 $N(R^a)C(=O)R^c$,

- 5 -



5

and N(R^a)SO₂R^c, and when X is SO₂C(R^a)=CR^a, Y additionally can be aryl and heteroaryl;

10 R^a is selected from the group consisting of hydrogen, C₁₋₆alkyl, cyano, aryl, arylC₁₋₃alkyl, C₁₋₃alkylenearyl, heteroaryl, heteroarylC₁₋₃alkyl, and C₁₋₃alkyleneheteroaryl;

15 R^b is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₃alkyleneN(R^a)₂, aryl, arylC₁₋₃alkyl, C₁₋₃alkylenearyl, and heteroaryl;

20 R^c is selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₁₋₃alkyleneN(R^a)₂, C₁₋₆alkylenearyl, C₁₋₆alkyleneHet, haloC₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈heterocycloalkyl, Het, C₁₋₃alkyleneheteroaryl, C₁₋₆alkyleneC(=O)OR^a, and C₁₋₃alkyleneC₃₋₈heterocycloalkyl;

25 or R^a and R^c are taken together to form a 5- or 6-membered ring, optionally containing at least one heteroatom;

30 Q is O, S, or NR^d;
B is O, S, or NR^d;
C is O, S, or NR^a;
D is CR^a or N;
E is CR^a, C(R^a)₂, or NR^d; and

R^d is null or is selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, heteroaryl,

- 6 -

arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₁₋₃alkylenearyl,
and C₁₋₃alkyleneheteroaryl;

Het represents a 5- or 6-membered
heterocyclic ring, saturated or partially or fully
5 unsaturated, containing at least one heteroatom
selected from the group consisting of oxygen,
nitrogen, and sulfur, and optionally substituted
with C₁₋₄alkyl or C(=O)OR^a;

n is 0, 1, 2, 3, or 4;

10 q is 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts and
solvates (e.g., hydrates) thereof.

As used herein, the term "alkyl" includes
straight chained and branched hydrocarbon groups
15 containing the indicated number of carbon atoms,
typically methyl, ethyl, and straight chain and
branched propyl and butyl groups. The hydrocarbon
group can contain up to 16 carbon atoms. The term
"alkyl" includes "bridged alkyl," i.e., a C₆-C₁₆
20 bicyclic or polycyclic hydrocarbon group, for
example, norbornyl, adamantyl, bicyclo[2.2.2]octyl,
bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, or deca-
hydronaphthyl. The term "cycloalkyl" is defined as
a cyclic C₃-C₈ hydrocarbon group, e.g., cyclopropyl,
25 cyclobutyl, cyclohexyl, and cyclopentyl.

The term "alkenyl" is defined identically
as "alkyl," except for containing a carbon-carbon
double bond. "Cycloalkenyl" is defined similarly to
cycloalkyl, except a carbon-carbon double bond is
30 present in the ring.

The term "alkylene" refers to an alkyl
group having a substituent. For example, the term
"C₁₋₃alkylenearyl" refers to an alkyl group contain-

- 7 -

ing one to three carbon atoms, and substituted with an aryl group. The term "alkenylene" as used herein is similarly defined, and contains the indicated number of carbon atoms and a carbon-carbon double bond, and includes straight chained and branched alkenylene groups, like ethylenylene.

The term "halo" or "halogen" is defined herein to include fluorine, bromine, chlorine, and iodine.

The term "haloalkyl" is defined herein as an alkyl group substituted with one or more halo substituents, either fluoro, chloro, bromo, iodo, or combinations thereof. Similarly, "halocycloalkyl" is defined as a cycloalkyl group having one or more halo substituents.

The term "aryl," alone or in combination, is defined herein as a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl. Unless otherwise indicated, an "aryl" group can be unsubstituted or substituted, for example, with one or more, and in particular one to three, halo, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfenyl, and alkylsulfonyl. Exemplary aryl groups include phenyl, naphthyl, tetrahydronaphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, and the like. The terms "aryl_{C₁₋₃}alkyl" and "heteroaryl_{C₁₋₃}alkyl" are defined as an aryl or heteroaryl group having a C₁₋₃alkyl substituent.

- 8 -

The term "heteroaryl" is defined herein as a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkyl-
sulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include thienyl, furyl, pyridyl, oxazolyl, quinolyl, isoquinolyl, indolyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl.

The term "Het" is defined as monocyclic, bicyclic, and tricyclic groups containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. A "Het" group also can contain an oxo group (=O) attached to the ring. Nonlimiting examples of Het groups include 1,3-dioxolane, 2-pyrazoline, pyrazolidine, pyrrolidine, piperazine, a pyrroline, 2H-pyran, 4H-pyran, morpholine, thiopholine, piperidine, 1,4-dithiane, and 1,4-dioxane.

The term "hydroxy" is defined as -OH.

The term "alkoxy" is defined as -OR, wherein R is alkyl.

The term "alkoxyalkyl" is defined as an alkyl group wherein a hydrogen has been replaced by an alkoxy group. The term "(alkylthio)alkyl" is defined similarly as alkoxyalkyl, except a sulfur atom, rather than an oxygen atom, is present.

- 9 -

The term "hydroxyalkyl" is defined as a hydroxy group appended to an alkyl group.

The term "amino" is defined as -NH_2 , and the term "alkylamino" is defined as -NR_2 , wherein at least one R is alkyl and the second R is alkyl or hydrogen.

The term "acylamino" is defined as RC(=O)N , wherein R is alkyl or aryl.

The term "alkylthio" is defined as -SR , wherein R is alkyl.

The term "alkylsulfinyl" is defined as R-SO_2 , wherein R is alkyl.

The term "alkylsulfonyl" is defined as R-SO_3 , wherein R is alkyl.

The term "nitro" is defined as -NO_2 .

The term "trifluoromethyl" is defined as -CF_3 .

The term "trifluoromethoxy" is defined as -OCF_3 .

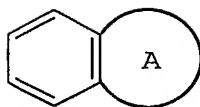
The term "spiro" as used herein refers to a group having two carbon atoms directly bonded to the carbon atom to which R^1 is attached.

The term "cyano" is defined as -CN .

In a preferred embodiment, q is 0. In other preferred embodiments, R^0 is selected from the group consisting of aryl, Het, OR^a , C(=O)OR^a , C_{1-4} -alkylene NR^aR^b , OC(=O)R^a , C(=O)R^a , NR^aR^b , C_{3-8} cycloalkyl, C_{3-8} cycloalkylQ, $\text{C(=O)NR}^a\text{R}^b$, and $\text{C(=O)NR}^a\text{R}^c$.

In a preferred group of compounds of formula (I), R^1 is represented by

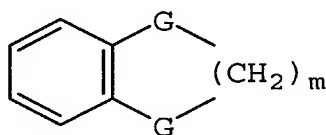
- 10 -



5

wherein the bicyclic ring can represent, for example, naphthalene or indene, or a heterocycle, such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene, or benzofuran, or

10



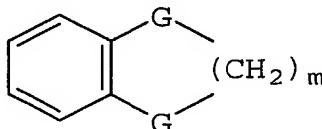
15

wherein m is an integer 1 or 2, and G , independently, is $C(R^a)_2$, O , S , or NR^a . The bicyclic ring comprising the R^1 substituent typically is attached to the rest of the molecule by a phenyl ring carbon atom.

20

In another preferred group of compounds of formula (I), R^1 is represented by an optionally substituted bicyclic ring

25

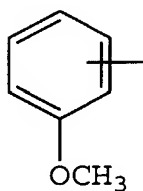


30

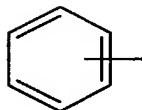
- 11 -

wherein m is 1 or 2, and G, independently, are $C(R^a)_2$ or O. Especially preferred R^1 substituents include

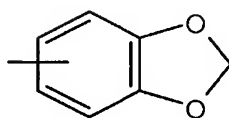
5



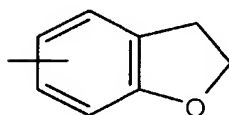
10



15

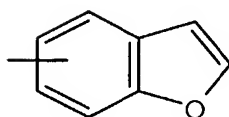


20



25

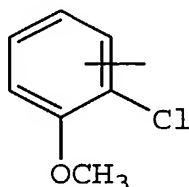
, and



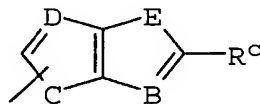
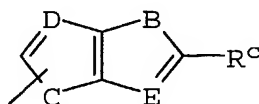
30

- 12 -

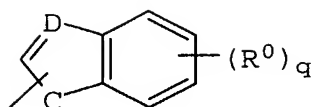
Within this particular group of compounds, nonlimiting examples of substituents for the bicyclic ring include halogen (e.g., chlorine), C₁₋₃alkyl (e.g., methyl, ethyl, or i-propyl), OR^a (e.g., methoxy, ethoxy, or hydroxy), CO₂R^a, halomethyl or halomethoxy (e.g., trifluoromethyl or trifluoromethoxy), cyano, nitro, and NR^aR^b. For example, R¹ can be



In other preferred embodiments, R¹ is optionally substituted and selected from the group consisting of C₁₋₄alkyleneQR^a, C₁₋₄alkyleneQC₁₋₄alkyleneQR^a, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, C₁₋₆alkyl,

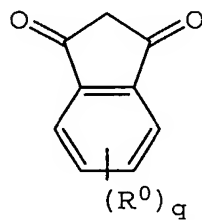


- 13 -



, and

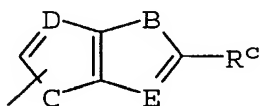
5



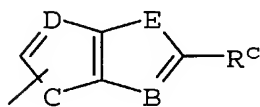
10

In a more preferred group of compounds of
 formula (I), R^1 is represented by

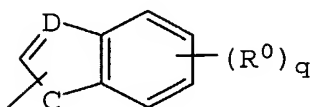
15



20



25

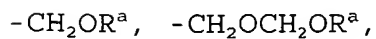
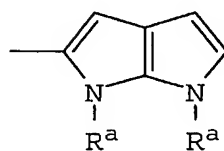
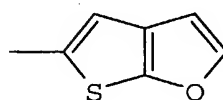
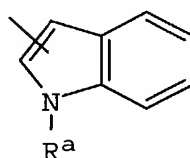
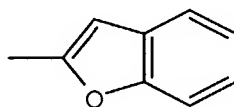
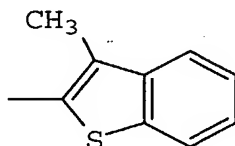


30

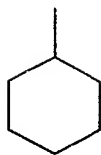
- 14 -

C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, C₁₋₆alkyl, C₁₋₄alkyleneQR^a, and C₁₋₄alkyleneQC₁₋₄alkyleneQR^a. A preferred Q is oxygen.

Some preferred R¹ substituents are

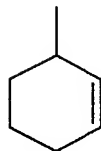


- 15 -



5

, and



10

Within this particular group of compounds, preferred R^a substituents include hydrogen, C_{1-6} alkyl, and benzyl.

15

In a preferred embodiment, R^2 is selected from the group consisting of hydrogen, aryl, heteroaryl, OR^a , NR^aR^b , NR^aR^c , C_{1-4} alkyleneHet, C_{1-4} alkyleneheteroaryl, C_{1-4} alkylenearyl, C_{1-6} alkyl, C_{2-6} alkenyl, aryl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, $C(=O)R^a$, and $SO_2NR^aR^b$.

20

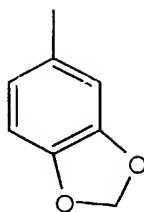
In preferred embodiments, R^3 is hydrogen, C_{1-6} alkyl, aryl, or heteroaryl.

25

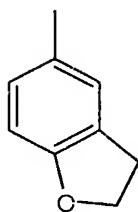
In especially preferred embodiments, q is 0 or R^0 is selected from the group consisting of halo, methyl, trifluoromethyl, and trifluoromethoxy; R^1 is selected from the group consisting of

- 16 -

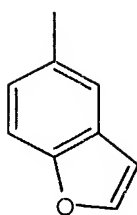
5



10

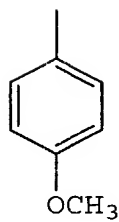


15

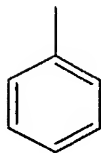


20

25

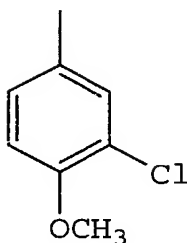


- 17 -



5

, and



10

15

R^2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, NR^aR^c , and C_{1-4} alkyleneHet;

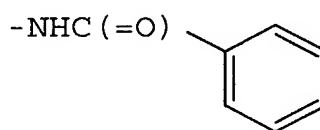
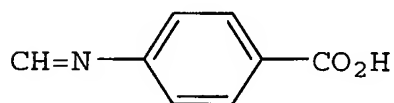
X is selected from the group consisting of $C(=O)$, $C(=S)$, and $SO_2CH=CH$;

20

Y is selected from the group consisting of $C(R^a)=NR^c$, $C(=O)N(R^a)(CH_2)_n(R^c)$, $N(R^b)(CH_2)_n(R^c)$, $N(R^a)C(=O)R^c$, $N(R^a)SO_2R^c$, $O(CH_2)_nR^c$, aryl when X is $SO_2CH=CH$, $(CH_2)_nC(=O)OR^c$, $(CH_2)_n$ aryl, and $(CH_2)_nC(=O)R^c$.

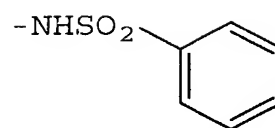
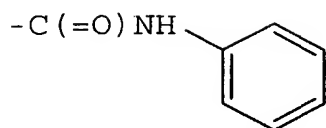
In other preferred embodiments, Y is selected from the group consisting of

25

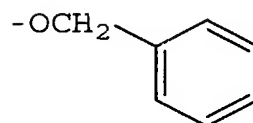
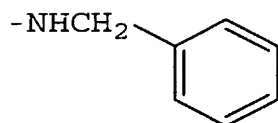


30

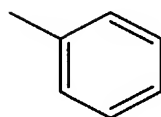
- 18 -



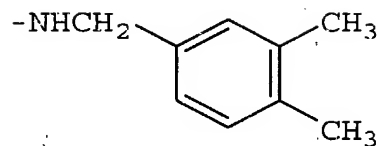
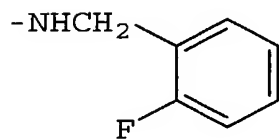
5



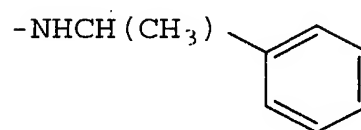
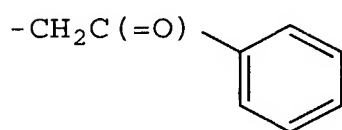
10

, when X is $\text{SO}_2\text{CH}=\text{CH}$

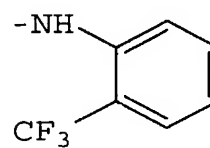
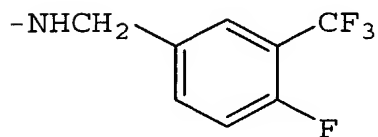
15



20

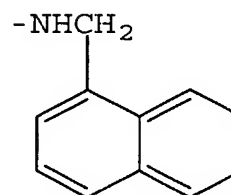
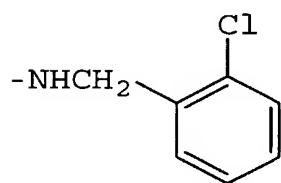
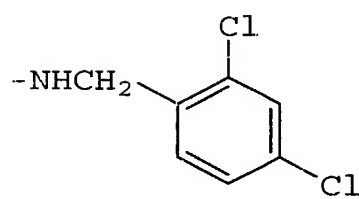
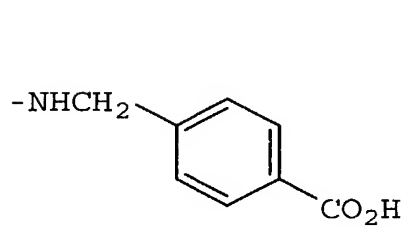
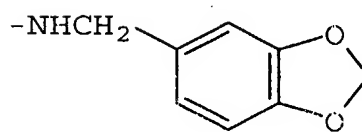
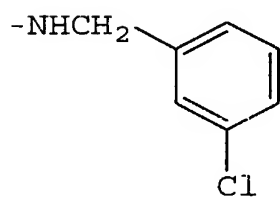
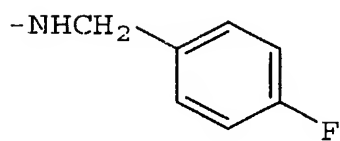
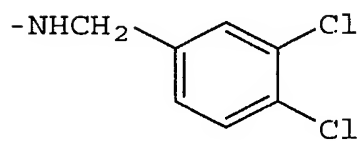
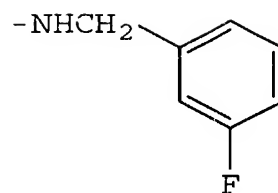
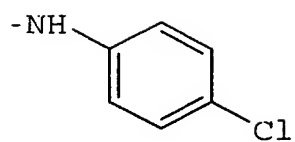


25

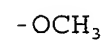
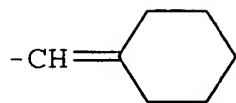


30

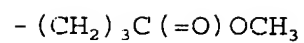
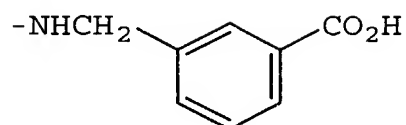
- 19 -



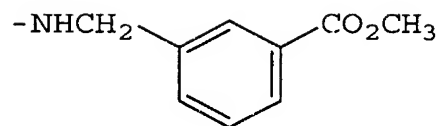
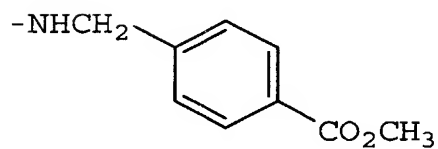
- 20 -



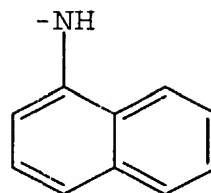
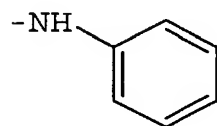
5



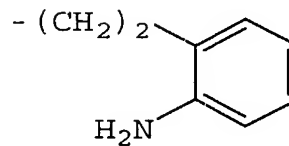
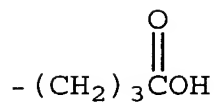
10



15



20



- 21 -

and

10

15 An especially preferred subclass of compounds within the general scope of formula (I) is represented by compounds of formula (II)

20

(II)

25 and pharmaceutically acceptable salts and solvates (e.g., hydrates) thereof.

30 Compounds of formula (I) can contain one or more asymmetric center, and, therefore, can exist as stereoisomers. The present invention includes both mixtures and separate individual stereoisomers

Patent provided by Sughrue Mion, PLLC - <http://www.sughrue.com>

- 22 -

of the compounds of formula (I). Compounds of formula (I) also can exist in tautomeric forms, and the invention includes both mixtures and separate individual tautomers thereof.

5 Pharmaceutically acceptable salts of the compounds of formula (I) can be acid addition salts formed with pharmaceutically acceptable acids. Examples of suitable salts include, but are not limited to, the hydrochloride, hydrobromide, sul-
10 fate, bisulfate, phosphate, hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts. The compounds of formula (I) also can
15 provide pharmaceutically acceptable metal salts, in particular alkali metal salts and alkaline earth metal salts, with bases. Examples include the sodium, potassium, magnesium, and calcium salts.

 Compounds of the present invention are
20 potent and selective inhibitors of cGMP-specific PDE5. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where selective inhibition of PDE5 is considered to be beneficial.

25 Phosphodiesterases (PDEs) catalyze the hydrolysis of cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). The PDEs have been classified into at least seven isoenzyme families and are
30 present in many tissues (J.A. Beavo, *Physiol. Rev.*, 75, p. 725 (1995)).

 PDE5 inhibition is a particularly attractive target. A potent and selective inhibitor of

- 23 -

PDE5 provides vasodilating, relaxing, and diuretic effects, all of which are beneficial in the treatment of various disease states. Research in this area has led to several classes of inhibitors based on the cGMP basic structure (E. Sybertz et al., *Expert. Opin. Ther. Pat.*, 7, p. 631 (1997)).

The biochemical, physiological, and clinical effects of PDE5 inhibitors therefore suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocytopenia, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, peptic ulcer, male erectile dysfunction, female sexual dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

An especially important use is the treatment of male erectile dysfunction, which is one form of impotence and is a common medical problem. Impotence can be defined as a lack of power, in the

- 24 -

male, to copulate, and can involve an inability to achieve penile erection or ejaculation, or both. The incidence of erectile dysfunction increases with age, with about 50% of men over the age of 40 suffering from some degree of erectile dysfunction.

In addition, a further important use is the treatment of female arousal disorder. Female arousal disorders are defined as a recurrent inability to attain or maintain an adequate lubrication/swelling response of sexual excitement until completion of sexual activity. The arousal response consists of vasocongestion in the pelvis, vaginal lubrication, and expansion and swelling of external genitalia.

It is envisioned, therefore, that compounds of formula (I) are useful in the treatment of male erectile dysfunction and female arousal disorder. Thus, the present invention concerns the use of compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal and arousal disorder in a female animal, including humans.

The term "treatment" includes preventing, lowering, stopping, or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment" includes both medical therapeutic and/or prophylactic administration, as appropriate.

It also is understood that "a compound of formula (I)," or a physiologically acceptable salt

- 25 -

or solvate thereof, can be administered as the neat compound, or as a pharmaceutical composition containing either entity.

5 Although the compounds of the invention are envisioned primarily for the treatment of sexual dysfunction in humans, such as male erectile dysfunction and female arousal disorder, they also can be used for the treatment of other disease states.

10 A further aspect of the present invention, therefore, is providing a compound of formula (I) for use in the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, acute respiratory distress
15 syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-PTCA or post-bypass graft stenosis), peripheral vascular disease, vascular disorders such as Raynaud's disease, thrombocythemia, inflammatory
20 diseases, prophylaxis of myocardial infarction, prophylaxis of stroke, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction,
25 or diseases characterized by disorders of gut motility (e.g., IBS).

30 According to another aspect of the present invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of the above-noted conditions and disorders.

 In a further aspect, the present invention provides a method of treating the above-noted con-

- 26 -

ditions and disorders in a human or nonhuman animal body which comprises administering to said body a therapeutically effective amount of a compound of formula (I).

5 Compounds of the invention can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, 10 intramuscular, subcutaneous, and intracoronary) administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™.

 Oral administration of a compound of the 15 invention is the preferred route. Oral administration is the most convenient and avoids the disadvantages associated with other routes of administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after 20 oral administration, the drug can be administered parenterally, e.g., sublingually or buccally.

 Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the active ingredient is administered 25 in an effective amount to achieve its intended purpose. More specifically, a "therapeutically effective amount" means an amount effective to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination 30 of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

- 27 -

A "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from such data can be used in formulating a range of dosage for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the therapeutic effects.

The amount of composition administered is dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

- 28 -

Specifically, for administration to a human in the curative or prophylactic treatment of the conditions and disorders identified above, oral dosages of a compound of formula (I) generally are about 0.5 to about 1000 mg daily for an average adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

For human use, a compound of formula (I) can be administered alone, but generally is administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of formula (I) into preparations which can be used pharmaceutically.

- 29 -

These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a compound of the present invention is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition can additionally contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 5% to about 95% compound of the present invention, and preferably from about 25% to about 90% compound of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.5% to about 90% by weight of a compound of the present invention, and preferably about 1% to about 50% of a compound of the present invention.

When a therapeutically effective amount of a compound of the present invention is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stabil-

- 30 -

ity, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound of the present invention, an isotonic vehicle.

For oral administration, the compounds can be formulated readily by combining a compound of formula (I) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound of formula (I) with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

For administration by inhalation, compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

- 31 -

The compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Compounds of the present invention also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by

- 32 -

implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Many of the compounds of the present invention can be provided as salts with pharmaceutically compatible counterions. Such pharmaceutically acceptable base addition salts are those salts that retain the biological effectiveness and properties of the free acids, and that are obtained by reaction with suitable inorganic or organic bases.

In particular, a compound of formula (I) can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

For veterinary use, a compound of formula (I) or a nontoxic salt thereof, is administered as a

- 33 -

suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I), together with a pharmaceutically acceptable diluent or carrier therefor. There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

In a particular embodiment, the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, or arousal disorder in a female animal, including humans, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula (I) can be prepared by any suitable method known in the art, or by the following processes which form part of the present invention. In the methods below, R^0 , R^1 , R^2 , and R^3 , as well as X and Y, are defined as in structural formula (I) above. In particular, compounds of structural formula (I) can be prepared according to the synthetic schemes illustrated in the following examples.

- 34 -

It should be understood that protecting groups can be utilized in accordance with general principles of synthetic organic chemistry to provide compounds of structural formula (I). Protecting group-forming reagents, like benzyl chloroformate and trichloroethyl chloroformate, are well known to persons skilled in the art, for example, see T.W. Greene et al., "Protective Groups in Organic Synthesis, Third Edition," John Wiley and Sons, Inc., NY, NY (1999). These protecting groups are removed when necessary by appropriate basic, acidic, or hydrolytic conditions known to persons skilled in the art. Accordingly, compounds of structural formula (I) not specifically exemplified herein can be prepared by persons skilled in the art.

In addition, compounds of formula (I) can be converted to other compounds of formula (I). Thus, for example, a particular R substituent can be interconverted to prepare another suitably substituted compound of formula (I). Examples of appropriate interconversions include, but are not limited to, OR^a to hydroxy by suitable means (e.g., using an agent such as SnCl₂ or a palladium catalyst, like palladium-on-carbon), or amino to substituted amino, such as acylamino or sulphonylamino, using standard acylating or sulfonylating conditions.

Compounds of formula (I) can be prepared as individual stereoisomers or as a racemic mixture. Individual stereoisomers of the compounds of the invention can be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent stereoisomers, for example, using HPLC on a chiral

- 35 -

column, such as Hypersil naphthyl urea, or using separation of salts of stereoisomers. Compounds of the invention can be isolated in association with solvent molecules by crystallization from, or
5 evaporation of, an appropriate solvent.

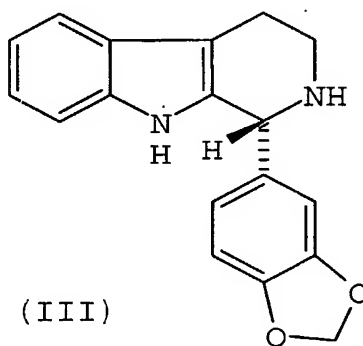
The pharmaceutically acceptable acid addition salts of the compounds of formula (I) that contain a basic center can be prepared in a conventional manner. For example, a solution of the free base
10 can be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be ob-
15 tained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques. Thus, according to a further aspect of the invention, a method
20 for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) is provided, followed by (i) salt formation, or (ii) solvate (e.g., hydrate) formation.

The following additional abbreviations are
25 used hereafter in the accompanying examples: rt (room temperature), min (minute), h (hour), g (gram), sat (saturated), mmol (millimole), m.p. (melting point), LiOH (lithium hydroxide), eq (equivalents), L (liter), mL (milliliter), μ L
30 (microliter), DMSO (dimethyl sulfoxide), CH_2Cl_2 (dichloromethane), IPA (isopropyl alcohol), TFA (trifluoroacetic acid), EtOH (ethanol), MeOH (methanol), DMF (dimethylformamide), EtOAc (ethyl

- 36 -

acetate), Na_2SO_4 (sodium sulfate), HCl (hydrochloric acid), M (molar), N (normal), KOH (potassium hydroxide), MgSO_4 (magnesium sulfate), NaHCO_3 (sodium bicarbonate), NaCl (sodium chloride), Ac_2O (acetic anhydride), Et_3N (triethylamine), AcOH (acetic acid), and THF (tetrahydrofuran).

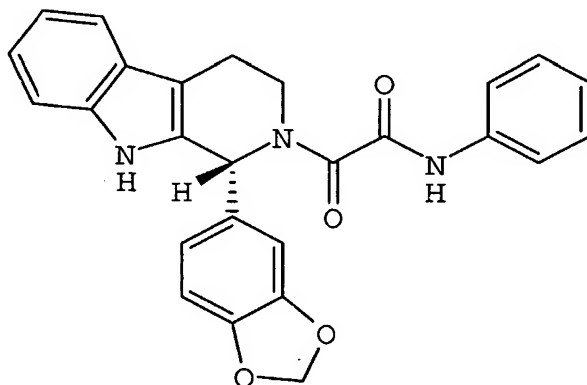
Many of the following examples were prepared from the compound of structural formula (III), i.e., 1-benzo[1,3]dioxol-5-yl-2,3,4,9-tetrahydro-1H- β -carboline. The synthesis of compound (III) is disclosed in Bombrun U.S. Patent No. 6,117,881, incorporated herein in its entirety by reference. Compounds analogous to compound (III), but having a different R^1 group can be synthesized in an identical or similar manner as compound (III) by utilizing appropriate R^1CHO starting material.



- 37 -

Example 1

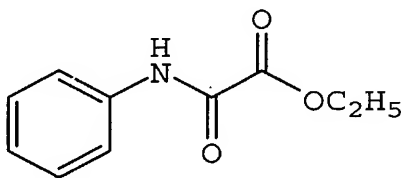
(1R)-2-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-2-oxo-N-phenylacetamide



Example 1

Example 1 was prepared from carboline (III) using the following synthetic sequence.

Preparation of N-phenyloxalamic acid ethyl ester (Intermediate 1)

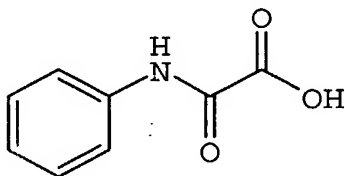


Aniline (3.4 g, 37 mmol) was dissolved in pyridine (50 mL), then ethyl chloroxoacetate (5.0 g, 37 mmol) was added to the resulting solution dropwise. The resulting mixture was stirred at room temperature for 48 hours, then diluted with water

- 38 -

and extracted twice with EtOAc. The combined organic extracts were washed with 1N HCl, water, brine, then dried (Na_2SO_4) and concentrated to provide 5.8 g (81%) of an oil that crystallized on standing. ^1H -NMR ($\text{DMSO}-d_6$) δ : 1.3 (t, $J=7$ Hz, 3H), 4.3 (q, $J=7$ Hz, 2H), 7.1-7.8 (m, 5H), 10.7 (s, 1H); MS ES+m/e 194.2 (p+1), ES-m/e 192.3 (p-1).

Preparation of N-phenyloxalamic acid
(Intermediate 2)



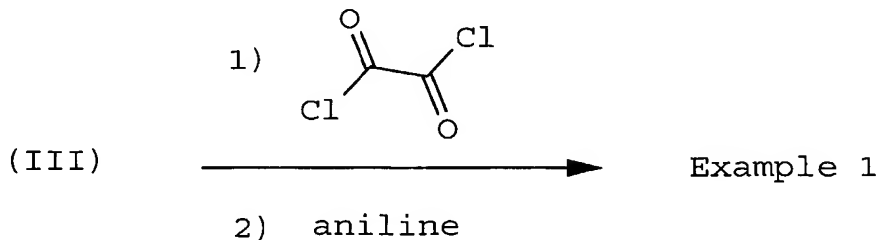
A solution of KOH (1.68 g, 30 mmol) in water (25 mL) and MeOH (25 mL) was added to Intermediate 1 (5.8 g, 30 mmol), and the resulting mixture was stirred for 18 hours at room temperature. The reaction was diluted with water, then extracted with EtOAc. The aqueous layer was cooled in an ice bath, acidified with 1N HCl, extracted with EtOAc, dried (Na_2SO_4), and concentrated *in vacuo* to provide 3.8 g (77%) of a colorless solid. ^1H NMR ($\text{DMSO}-d_6$) δ : 7.1-7.8 (m, 6H), 10.5 (s, 1H); MS ES+m/e 166.0 (p+1), ES-m/e 164.1 (p-1). Anal. Calcd for $\text{C}_8\text{H}_7\text{NO}_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.99; H, 4.25; N, 8.46.

- 39 -

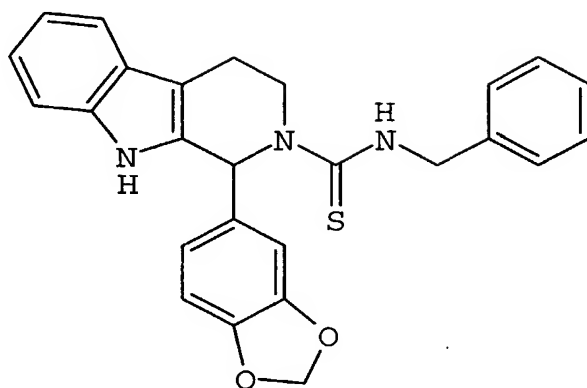
Preparation of Example 1

A mixture of Compound (III) (1.0 g, 3.4 mmol), Intermediate 2 (561 mg, 3.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (671 mg, 3.5 mmol), and 4-dimethylaminopyridine (50 mg) dissolved in CH_2Cl_2 (25 mL) was stirred for 18 hours at room temperature. The reaction was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to provide 1.4 g of crude product. Chromatography (silica gel, 30% EtOAc/70% hexanes) provided 450 mg (30%) of Example 1 as a foam. ^1H NMR ($\text{DMSO}-d_6$) δ : 2.92 (dd, $J=4$, 15 Hz, 1H), 3.15 (dt, $J=4$, 12 Hz, 2H), 3.45 (dt, $J=4$, 12 Hz, 1H), 5.27 (dd, $J=4$, 13 Hz, 1H), 5.9 (s, 2H), 6.7-7.8 (m, 13H), 9.2 (s, 1H); MS ES+m/e 440.2 (p+1), ES-m/e 438.2 (p-1). Anal. Calcd for $\text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 70.70; H, 4.86; N, 9.4. Chiral HPLC (Chiralcel OD, 5-50% isopropylamine in heptane over 30 minutes): >95% ee.

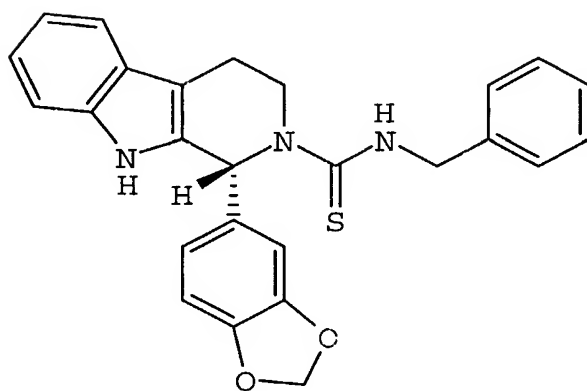
Example 1 also can be prepared by the following synthetic sequence:



- 40 -

Examples 2a and 2b

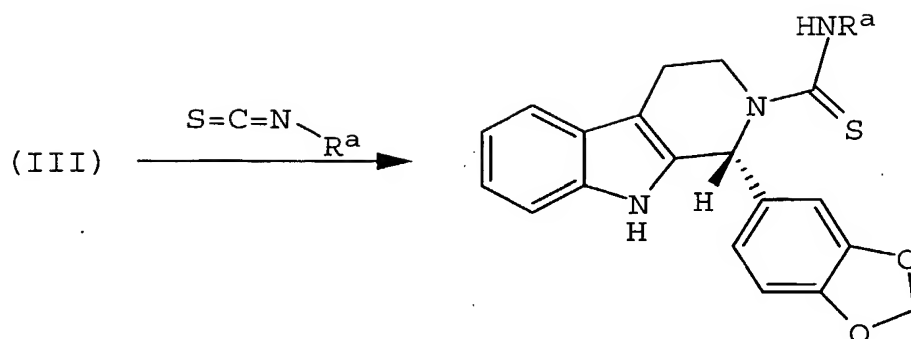
Example 2a



Example 2b

Examples 2a and 2b were synthesized by the following general procedure for the preparation of thioureas utilizing compound (III) as the starting material.

- 41 -



General Procedure

5 An isothiocyanate (3.4 mmol, 1.01 eq) was added to a slurry of compound (III) in 5 mL of CH₂Cl₂ cooled in an ice bath. The ice bath was removed, then the mixture was stirred at room temperature for 3 hours. Methylene chloride was added to the mixture in a quantity sufficient to dissolve all solids, and the resulting solution was washed with 25 mL of 1M HCl and 25 mL of sat. NaHCO₃ solution. The organic phase then was dried over MgSO₄, and the resulting slurry filtered. The solvents were removed from the filtrate under vacuum to yield the crude product. Purification was achieved either by recrystallization from EtOH or by chromatography. Analysis for enantiomeric excess was accomplished using chiral HPLC (Chiracel OD, 5 to 50% isopropylamine in heptane over 30 minutes).

10

15

20

- 42 -

Preparation of Example 2a

Addition of benzyl isothiocyanate to compound (III) produced 1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid benzylamide (Example 2a) in 83% yield: mp 197°C. H^1 NMR (DMSO- d_6) δ : 11.0 (s, 1H), 8.5 (t, J=5 Hz, 1H), 7.8 (s, 1H), 7.6 (s, 1H), 7.43 (d, J=7 Hz, 1H), 7.4-7.28 m, 8H), 6.85 (dd, J=1.4, 8 Hz, 1H), 6.69 (d, J=8 Hz, 1H), 5.88 (s, 2H), 4.88 (overlapping dd, J=4.7, 14 Hz, 2H), 4.11 (dd, J=4.4, 14 Hz, 1H), 3.51-3.44 (m, 1H), 2.94-2.84 (m, 1H), 2.78 (dd, J=4, 15 Hz, 1H); MS ES+m/e 442 (p+1), ES-m/e 440 (p-1); IR (KBr, cm^{-1}): 1518, 1503, 1487; Elemental analysis: Anal. Calcd for $C_{26}H_{23}N_3O_2S$: C, 70.72; H, 5.25; N, 9.51. Found: C, 70.30; H, 5.27; N, 9.42.

Preparation of Example 2b

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid benzylamide

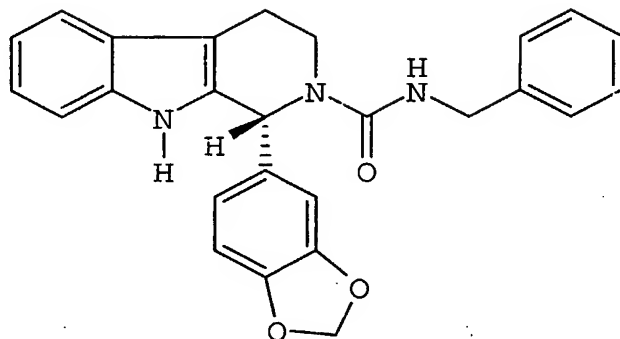
Addition of benzyl isothiocyanate to (1R)-benzo[1,3]dioxol-5-yl-2,3,4,9-tetrahydro-1H- β -carboline (1R isomer of compound (III)) provided Example 2b in 80% yield: mp 205-207°C. H^1 NMR (DMSO- d_6) δ : 11.0 (s, 1H), 8.5 (t, J=5 Hz, 1H), 7.8 (s, 1H), 7.6 (s, 1H), 7.43 (d, J=7 Hz, 1H), 7.4-7.28 (m, 8H), 6.85 (dd, J=1.4, 8 Hz, 1H), 6.69 (d, J=8 Hz, 1H), 5.88 (s, 2H), 4.88 (overlapping dd, J=4.7, 14 Hz, 2H), 4.11 (dd, J=4.4, 14 Hz, 1H), 3.51-3.44 (m, 1H), 2.94-2.84 (m, 1H), 2.78 (dd, J=4, 15 Hz, 1H); MS ES+m/e 442 (p+1), ES-m/e 440 (p-1); IR (KBr, cm^{-1}): 1518, 1503, 1487; Elemental analysis: Anal.

- 43 -

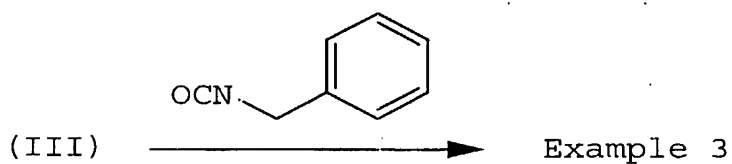
Calcd for $C_{26}H_{23}N_3O_2S$: C, 70.72; H, 5.25; N, 9.51.

Found: C, 70.30; H, 5.27; N, 9.42; 74% ee.

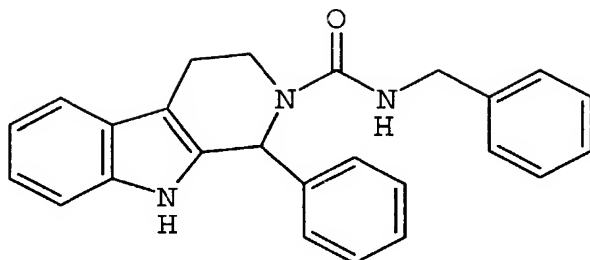
Example 3



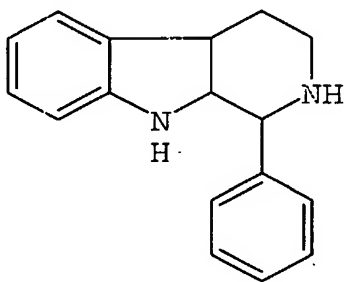
Example 3 was prepared by the following reaction, which is essentially identical to the reaction used to provide Examples 2a and 2b.



- 44 -

Example 4

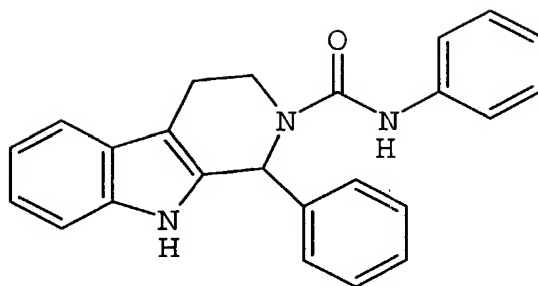
Example 4 was prepared in a manner identical to Example 3 using compound (IV) and benzyl isocyanate.



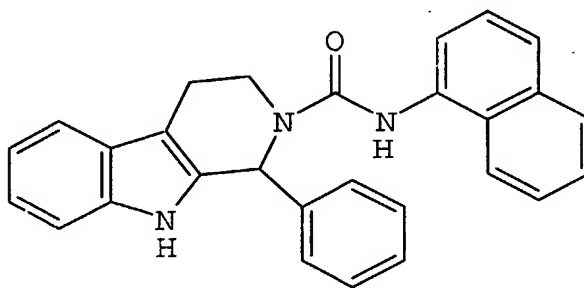
(IV)

Compound (IV) was prepared in a manner identical to compound (III) using benzaldehyde as a substitute for piperonal.

- 45 -

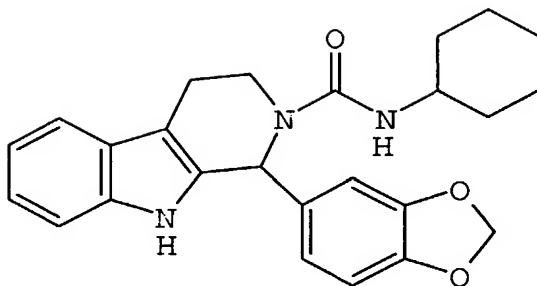
Example 5

Example 5 was prepared in a manner identical to Example 4 using compound (IV) and phenyl isocyanate.

Example 6

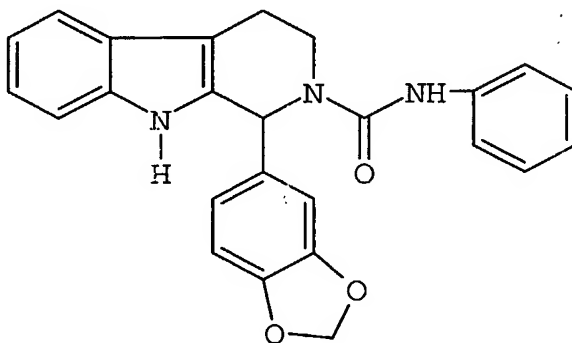
Example 6 was prepared in a manner identical to Example 4 using compound (IV) and 1-naphthyl isocyanate.

- 46 -

Example 7

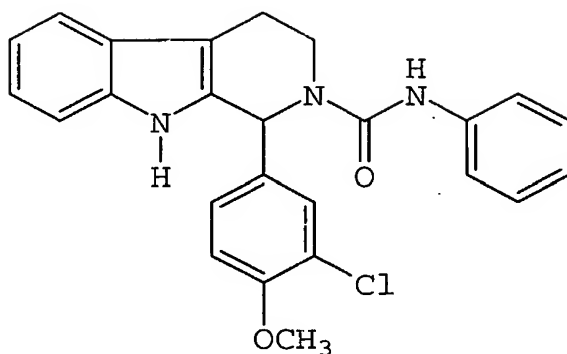
Example 7 was prepared in a manner identical to Example 3 using compound (III) and cyclohexyl isocyanate.

Examples 8 and 9 were prepared in a manner analogous to Examples 1-7.

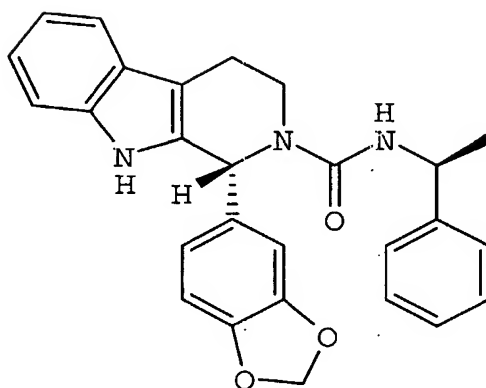
Examples 8 and 9

Example 8

- 47 -



Example 9

Example 10Preparation of Example 10

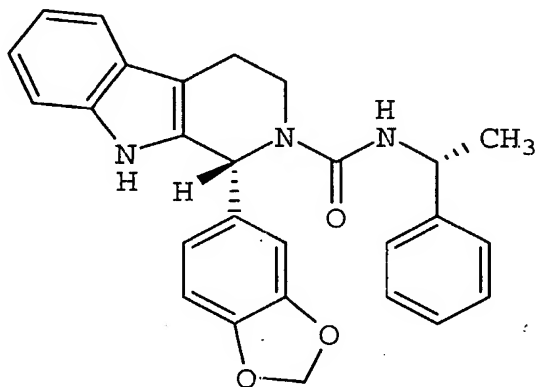
(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carboxylic acid (1S)-(phenylethyl) amide

Addition of (S)-α-methyl benzyl isocyanate to compound (III) provided Example 10 in 85% yield:

- 48 -

mp 120-121°C. ¹H NMR (DMSO-d₆) δ: 10.92, 10.90 (overlapping s, 1H), 7.46 (d, J=7 Hz, 1H), 7.39-6.97 (m, 8H), 6.85 (d, J=8 Hz, 1H), 6.75 (s, 1H), 6.62 (t, 9 Hz, 1H), 6.50 (d, J=10 Hz, 1H), 5.97, 5.98, 5.99 (overlapping 2, 2H), 4.96 (dq, J=7.0 7.6 Hz, 1H), 4.90 (dq, J=7.0 7.6 Hz, 1H), 4.20 broad (d, J=14 Hz, 1H), 3.12-3.02 (m, 1H), 2.89-2.60 (m, 2H), 1.40 (d, J=3 Hz, 3H); MS FAB 439 (m⁺); 100% ee.

Example 11



Preparation of Example 11

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carboxylic acid (1R)-(phenylethyl)amide

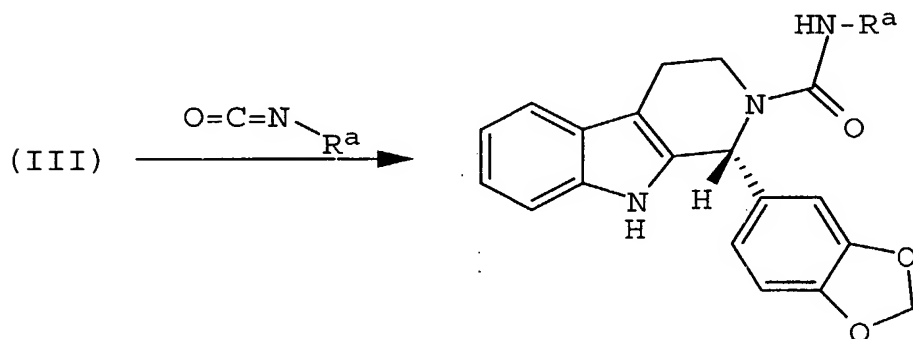
Addition of (R)-α-methylbenzyl isocyanate to compound (III) provided Example 11 in 83% yield. ¹H NMR (DMSO-d₆) δ: 10.92, 10.90 (overlapping s, 1H), 7.46 (d, J=7 Hz, 1H), 7.39-6.97 (m, 8H), 6.85 (d, J=8 Hz, 1H), 6.75 (s, 1H), 6.62 (t, 9 Hz, 1H), 6.50 (d, J=10 Hz, 1H), 5.97, 5.98, 5.99 (overlapping

- 49 -

s, 2H), 4.96 (dq, $J=7.0$ 7.6 Hz, 1H), 4.90 (dq, $J=7.0$ 7.6 Hz, 1H), 4.20 (broad d, $J=14$ Hz, 1H), 3.12-3.02 (m, 1H), 2.89-2.60 (m, 2H), 1.40 (d, $J=3$ Hz, 3H); MS ES+m/e 440 (p+1), ES-m/e (438 p-1); 82% ee.

5

The following is a general procedure for the preparation of ureas utilizing compound (III) as the starting material:

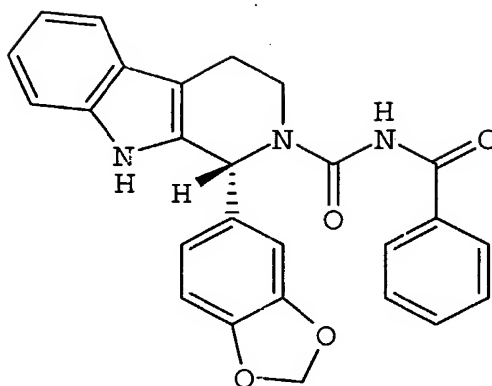


10

The isocyanate $R^aN=C=O$ (3.5 mm, 1.1 eq) was added to a stirred slurry of compound (III) in 5 mL of CH_2Cl_2 at room temperature. The resulting reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under vacuum, then the crude reaction mixture purified by chromatography (10% CH_2Cl_2 in hexane followed by 50% EtOAc in hexane). The product was isolated by removal of the solvent from the combined fractions containing only the desired product.

20

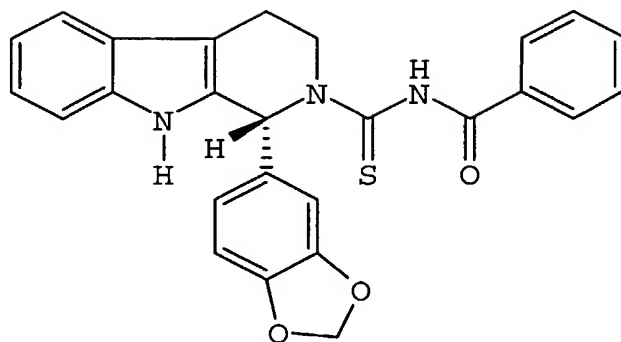
- 50 -

Example 12

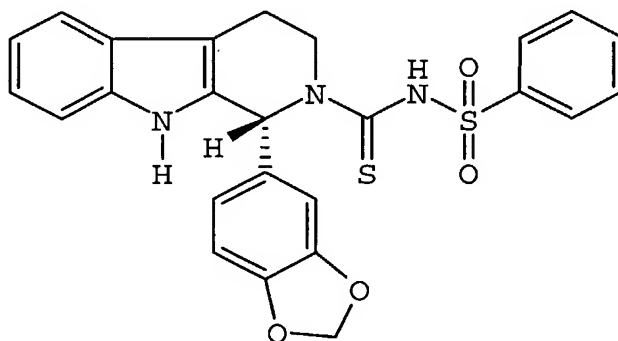
Preparation of N-((1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carbonyl)benzamide (Example 12)

Addition of benzoyl isocyanate to the (R)-isomer of compound (III) provided Example 12 in 79% yield. ¹H NMR (DMSO-d₆) δ: 10.98 (s, 1H), 10.40 (broad s, 1H), 7.89 (d, J=7 Hz, 2H), 7.63-7.46 (m, 4H), 7.32 (d, J=8 Hz, 1H), 7.12-7.01 (m, 2H), 6.89 (d, J=8 Hz, 2H), 6.73 (d, J=8 Hz, 1H), 6.54 (broad s, 1H), 6.02 (s, 2H), 4.10 (br s, 1H), 3.38-3.21 (m, 1H), 2.98-2.90 (m, 1H), 2.78 (dd, J=2, 12 Hz, 1H); MS ES+m/e 440 (p+1), ES-m/e 438 (p-1); Anal. Calcd for C₂₆H₂₁N₃O₄: C, 71.06; H, 4.81; N, 9.56. Found: C, 71.01; H, 4.92; N, 9.50; 90% ee.

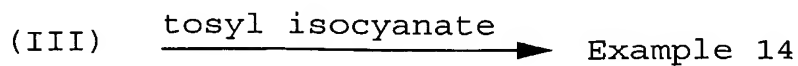
- 51 -

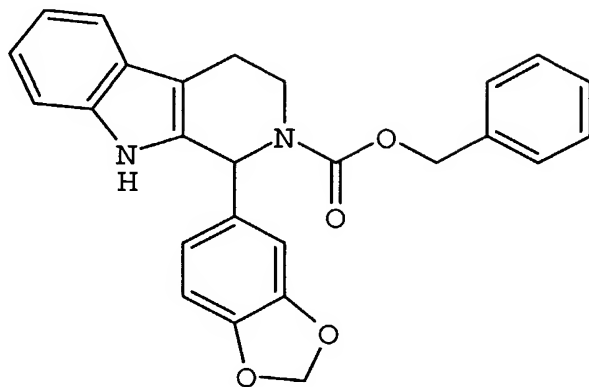
Example 13

Example 13 was prepared in a manner similar to Example 12 using compound (III) and benzoyl isothiocyanate.

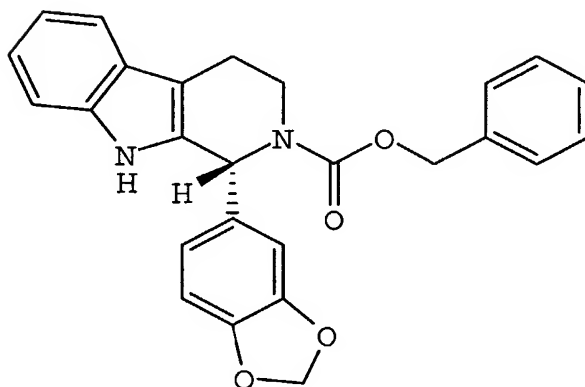
Example 14

Example 14 is prepared by the following synthetic procedure.



Examples 15a and 15b

Example 15a



Example 15b

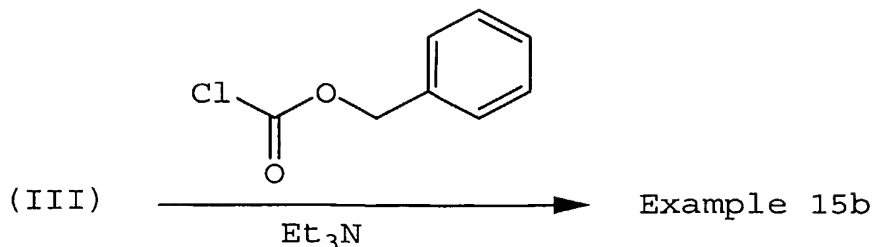
Preparation of 1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid benzyl ester (Example 15a)

Example 15a was prepared by the following general procedure for the preparation of acylated compounds utilizing compound (III).

- 53 -

Benzyl chloroformate (0.51 mL, 3.6 mmol) was added to a stirred slurry of compound (III) in 13 mL of anhydrous CH_2Cl_2 at room temperature. Triethylamine (0.50 mL, 3.6 mmol) was added, and stirring was continued for 1 hour. The reaction mixture was quenched with 15 mL of 1M HCl. The layers were separated, and the organic layer was washed with 15 mL of sat. NaHCO_3 solution. The layers were separated, and the organic phase was dried over MgSO_4 , filtered, and removed under vacuum to give crude Example 15a as a white foam. Purification via flash chromatography gave Example 15a 62% yield: mp 165-166°C. ^1H NMR ($\text{DMSO}-d_6$) δ : 10.85 (s, 1H), 7.45 (d, $J=7$ Hz, 1H), 7.42-7.26 (m, 5H), 7.3 (d, $J=8$ Hz, 1H), 7.28 (t, $J=1$, 7 Hz, 1H), 7.08 (t, $J=1$, 7Hz, 1H), 7.02 (d, $J=8$ Hz, 1H), 6.84 (d, $J=8$ Hz, 1H), 6.65 (d, $J=7$ Hz, 1H), 6.31 (br s, 1H), 5.98 (s, 2H), 5.22 (dd, $J=2$, 12 Hz, 1H), 5.18 (dd, $J=2$, 12 Hz, 1H), 4.22 (br d, $J=4.7$ Hz, 1H), 3.18-3.05 (m, 1H), 2.75 (m, 2H); MS ES+m/e 427 (p+1), ES-m/e 425 (p-1); IR (KBr, cm^{-1}) 1687.

Preparation of (1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid benzyl ester (Example 15b)

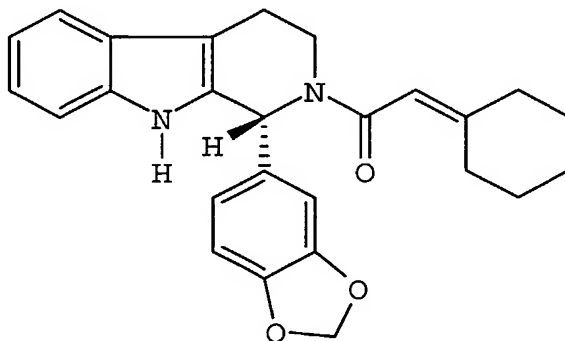


- 54 -

Example 15b was prepared from the R-isomer of compound (III) using the same procedure used in the synthesis of Example 15a to give 1.41 g (97% yield) of Example 15b as a white foam: mp 98-101°C.

¹H NMR (DMSO-d₆) δ: 10.85 (s, 1H), 7.45 (d, J=7 Hz, 1H), 7.42-7.26 (m, 5H), 7.3 (d, J=8 Hz, 1H), 7.28 (t, J=1, 7 Hz, 1H), 7.08 (t, J=1, 7 Hz, 1H), 7.02 (d, J=8 Hz, 1H), 6.84 (d, J=8 Hz, 1H), 6.65 (d, J=7 Hz, 1H), 6.31 (br s, 1H), 5.98 (s, 2H), 5.22 (dd, J=2, 12 Hz, 1H), 5.18 (dd, J=2, 12 Hz, 1H), 4.22 (br d, J=4.7 Hz, 1H), 3.18-3.05 (m, 1H), 2.75 (m, 2H); MS ES+m/e 427 (p+1), ES-m/e 425 (m-1); IR (KBr, cm⁻¹): 3399, 1633; Anal. Calcd for C₂₆H₂₂N₂O₄: C, 73.22; H, 5.19, N, 6.56. Found: C, 73.29; H, 5.26; N, 6.58; 93% ee.

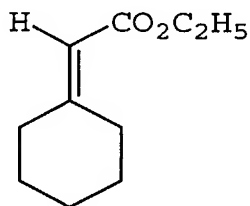
Example 16



Example 16 was prepared by the following synthetic sequence.

- 55 -

Preparation of cyclohexylideneacetic acid ethyl ester (Intermediate 3)



15 Triethylphosphonoacetate (5.0 g, 22.3 mmol) was dissolved in THF (25 mL) and cooled to -78°C under a nitrogen blanket. *n*-Butyllithium (1.6 M in hexanes, 13.9 mL, 22.3 mmol) was added dropwise via syringe followed by the addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (3 mL). The reaction was stirred at -78°C for 15

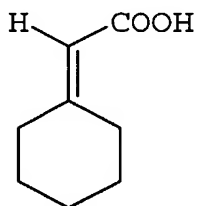
20 minutes. A solution of cyclohexanone (1.1 g, 11.2 mmol) dissolved in THF (5 mL) was added. The mixture was allowed to warm to room temperature, and stirred for 18 hours. The reaction was diluted with 1N HCl and extracted with EtOAc, then washed with

25 water, dried (Na₂SO₄), and concentrated *in vacuo* to provide 1.7 g (89%) of Intermediate 3 as an oil. ¹H NMR (DMSO-d₆) δ: 1.15 (t, J=7 Hz, 3H), 1.55 (br s, 6H), 2.2 (br s, 2H), 2.75 (br s, 2H), 4.05 (q, J=7 Hz, 2H), 5.6 (s, 1H).

30

- 56 -

**Preparation of cyclohexylideneacetic acid
(Intermediate 4)**

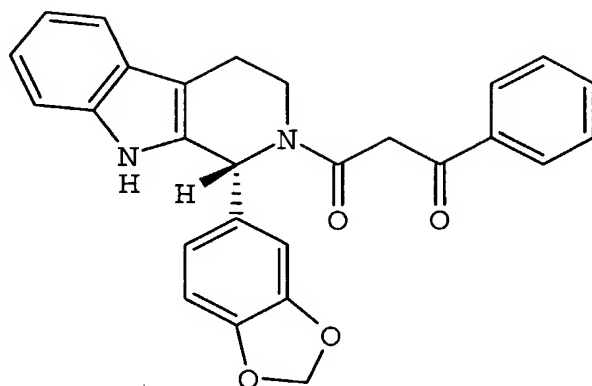
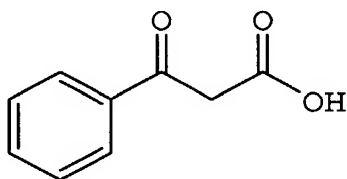


A mixture of KOH (1.0 g, 18 mmol) dissolved in water (25 mL) and Intermediate 3 (1.6 g, 9.5 mmol) dissolved in MeOH (5 mL) was stirred for 18 hours at room temperature. The reaction was refluxed for one hour, cooled, then extracted with EtOAc. The aqueous layer was acidified with 1N HCl and extracted with EtOAc, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to provide 1.3 g (100%) of Intermediate 4. ¹H NMR (DMSO-d₆) δ: 1.55 (br s, 6H), 2.1 (m, 2H), 2.8 (m, 2H), 5.5 (s, 1H), 11.9 (s, 1H); MS ES-m/e 139.1 (p-1).

Preparation of (1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carbolin-3-yl)-2-cyclohexylidene-ethanone (Example 16)

The addition of Intermediate 4 to the R-isomer of compound (III) provided 1.04 g (74%) of Example 16 as a solid. mp 116-118°C. ¹H NMR (DMSO-d₆) δ: 1.52 (m, 6H), 2.2 (m, 2H), 2.26 (m, 2H), 2.77 (m, 2H), 3.25 (dt, J=4, 12 Hz, 1H), 4.05 (dd, J=4, 12 Hz, 1H), 5.94 (s, 1H), 5.98 (s, 2H), 6.6-7.5 (m, 8H), 10.95 (s, 1H); MS ES+m/e 415.2 (p+1), ES-m/e 413.3 (p-1).

- 57 -

Example 17Preparation of 3-oxo-3-phenylpropionic acid
Intermediate 5)

Potassium hydroxide (1.25 g, 22 mmol) was dissolved in water (25 mL), then ethyl benzoylacetate (2.5 g, 13 mmol) was added to the KOH solution. The reaction mixture was stirred for 18 hours at room temperature, then cooled in a ice bath and acidified by a slow addition of 1N HCl. The resulting colorless precipitate was filtered to give 1.4 g (67%) of Intermediate 5 as a solid. ^1H NMR (DMSO- d_6) δ : 2.55 (s, 2H), 7.5-8.0 (m, 6H); MS ES+m/e 165.0 (p+1), ES-m/e 163.1 (p-1). Anal. Calcd

- 58 -

for $C_9H_8O_2$: C, 65.85; H, 4.91. Found: C, 65.66; H, 4.75.

5 Preparation of (1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-3-phenylpropane-1,3-dione (Example 17)

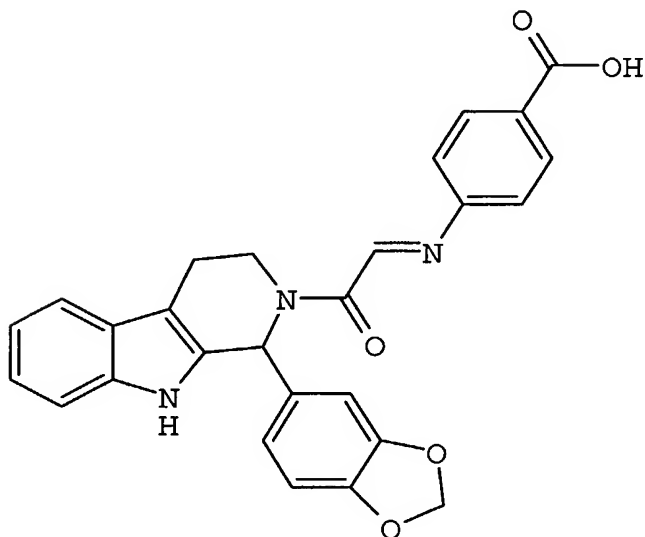
10 The addition of 3-oxo-3-phenylpropionic acid to the R-isomer of compound (III) provided 950 mg (63%) of Example 17 as a foam. 1H NMR ($DMSO-d_6$) δ : 2.93 (m, 2H), 3.45 (dt, $J=4$, 12 Hz, 1H), 4.00 (dd, $J=4$, 12 Hz, 1H), 4.15 (s, 1H), 5.94 (s, 2H), 6.6-8.0 (m, 15H); MS ES+m/e 439.2 (p+1), ES-m/e 15 437.2 (p-1); Chiral HPLC >95% ee.

Examples 18-23

20

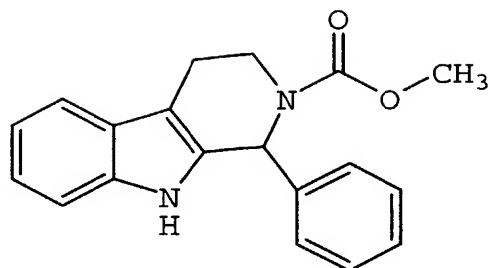
25

30

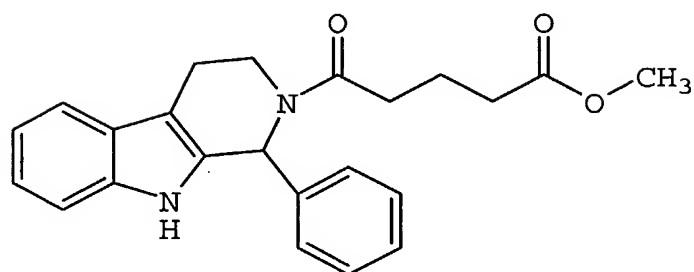


Example 18

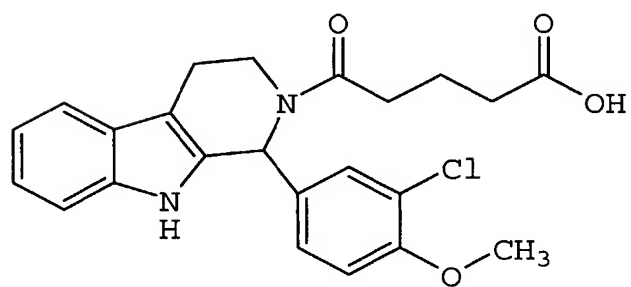
- 59 -



Example 19

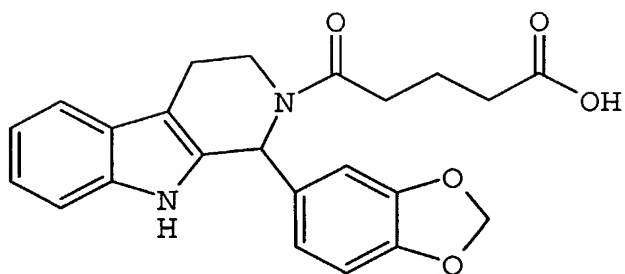


Example 20

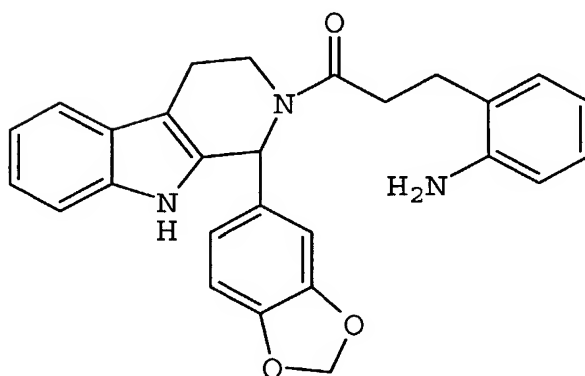


Example 21

- 60 -



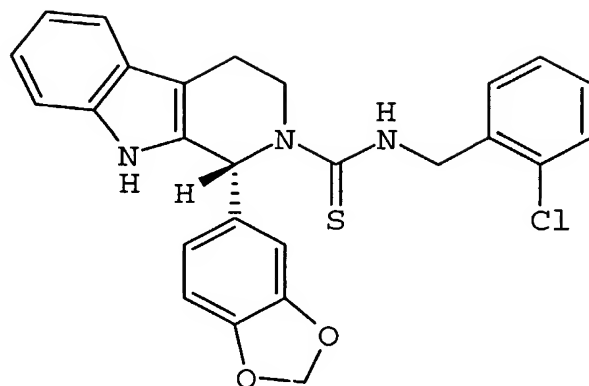
Example 22



Example 23

Examples 18-23 were prepared from compound (III) in a manner similar to Examples 1-17.

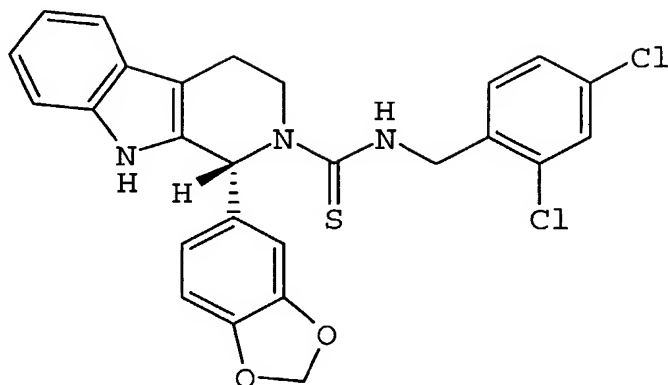
- 61 -

Example 24

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carbothioic acid 2-chlorobenzylamide (Example 24)

Addition of 2-chlorobenzyl isothiocyanate to the R-isomer of compound (III) provided Example 24 in 92% yield. mp 123-128°C. ¹H NMR (DMSO-d₆) δ: 11.08 (s, 1H), 8.50 (t, J=5 Hz, 1H), 7.76 (s, 1H), 7.49 (d, J=7 Hz, 1H), 7.43 (dd, J=1.6, 7 Hz, 1H), 7.32 (d, J=8 Hz, 1H), 7.29-7.18 (m, 3H), 7.12-6.98 (m, 3H) 6.88 (d, J=8 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 6.01, 6.00 (overlapping s, 2H), 5.02 (dd, J=5, 12 Hz, 1H), 4.84 (dd, J=5, 12 Hz, 1H), 4.49 (broad d, J=12 Hz, 1H), 3.37-3.27 (m, 1H), 3.01, 2.90 (m, 1H), 2.81 (dd, J=3, 15 Hz, 1H); MS ES+m/e 476 (p+1), ES-m/e 474 (p-1); 19% ee.

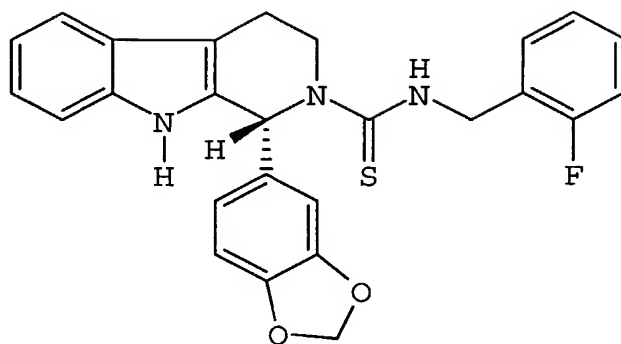
- 62 -

Example 25

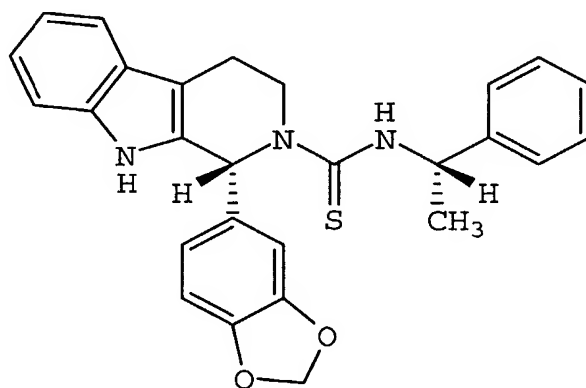
Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 2,4-dichlorobenzylamide (Example 25)

The addition of 2,4-dichlorobenzyl isothiocyanate to the R-isomer of compound (III) provided Example 25 in 100% yield. mp 124-127°C. ¹H NMR (DMSO-d₆) δ : 11.08 (s, 1H), 8.52 (t, J=5 Hz, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.49 (d, J=7 Hz, 1H), 7.39 (d, J=8 Hz, 1H), 7.12-6.98 (m, 5H), 6.89 (d, J=8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 6.01, 6.00 (overlapping s, 2H), 4.96 (dd, J=5, 16 Hz, 1H), 4.79 (dd, J=5, 16 Hz, 1H), 4.47 (broad d, J=12 Hz, 1H), 3.38-3.28 (m, 1H), 3.01, 2.91 (m, 1H), 2.79 (dd, J=3.15 Hz, 1H); MS ES+m/e 511 (p+1), ES-m/e 509 (p-1); 19% ee.

- 63 -

Example 26

Example 26 was prepared in a manner identical to Example 26 using 2-fluorobenzyl isothiocyanate.

Example 27

- 64 -

Preparation of (1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid ((S)-1-phenylethyl)amide (Example 27)

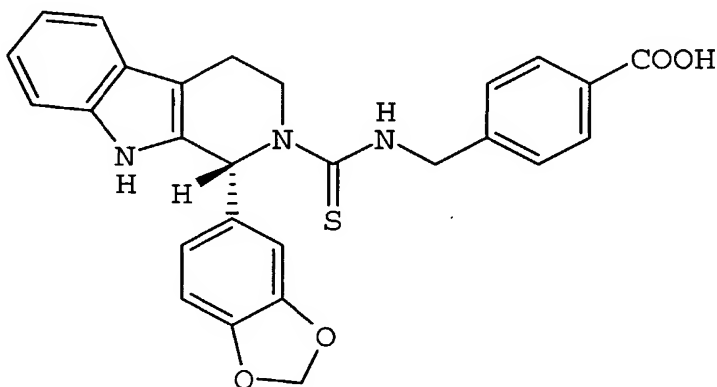
5

Example 27 (750 mg, 48%) was prepared by the same method given above for Example 23 from Compound (III) and (L)- α -methylbenzyl isothiocyanate. mp 117-121°C. ¹H NMR (DMSO-d₆) δ : 11.03 (s, 1H), 7.5-6.7 (m, 13H), 6.01 (d, J=3 Hz, 2H), 5.85 (5, J=5 Hz, 1H), 4.56 (br d, J=10 Hz, 1H), 3.35 (dd, J=3 Hz, 1H), 2.8 (dd, J=3, 10 Hz, 2H), 1.5 (d, J=5 Hz, 3H); MS ES+m/e 456.1 (p+1), ES-m/e 454.3 (p-1).

10

Example 28

15



20

25

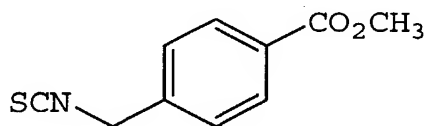
Example 28 was prepared by the following synthetic sequence.

30

- 65 -

**Preparation of 4-isothiocyanatomethylbenzoic acid
methyl ester (Intermediate 6)**

5



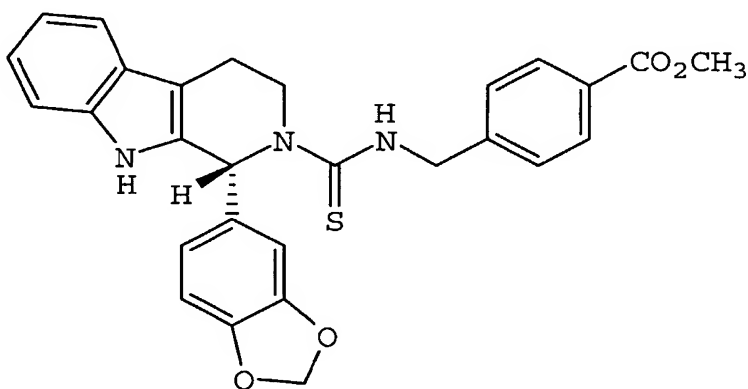
10

A mixture of 4-bromomethylbenzoic acid methyl ester (5.0 g, 21.8 mmol), potassium isothiocyanate (2.23 g, 25 mmol), and 18-crown-6 (158 mg, 0.06 mmol) suspended in 1,2-dichlorobenzene (100 mL) was heated at reflux for 2 hours. The mixture was cooled, then the solvent was evaporated. The residue was diluted with CH_2Cl_2 and filtered to remove solids. The filtrate was evaporated to give crude Intermediate 6 (8 g) which was used without purification.

20

- 66 -

Preparation of (1R)-4-{[(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbthioly1)-amino]methyl}benzoic acid methyl ester (Intermediate 7)



Crude Intermediate 6 (4 g) and the R-isomer of compound (III) (500 mg, 1.7 mmol) were dissolved in CH_2Cl_2 (25 mL), and the resulting mixture was stirred for 18 hours without cooling. The reaction mixture then was washed once with water, and the organic layer dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (silica gel, 30% EtOAc:70% hexanes) of the residue provided 370 mg (44%) of Intermediate 7 as a foam.

^1H NMR ($\text{DMSO}-d_6$) δ : 11.05 (s, 1H), 8.57 (t, $J=5$ Hz, 1H), 7.95-6.7 (m, 12H), 6.0 (s, 2H), 4.92 (ABq, $J=5$, 16 Hz, 2H), 4.4 (m, 1H), 3.84 (s, 3H), 3.3 (dt, $J=5$, 16 Hz, 1H), 2.85 (dt, $J=5$, 16 Hz, 1H), 2.75 (dd, $J=5$, 16 Hz, 1H); MS ES+m/e 500.1 ($p+1$), ES-m/e 498.2 ($p-1$); IR (KBr, cm^{-1}): 1719, 1521, 1503, 1488; Anal. Calcd. for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$: C, 67.31; H, 5.04; N, 8.41. Found: C, 66.95; H, 4.88; N, 8.19.

- 67 -

Preparation of (1R)-4-{[(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbthioly1)-amino]methyl}benzoic acid (Example 28)

5

A mixture of Intermediate 7 (350 mg, 0.7 mmol) and LiOH (18 mg, 0.75 mmol) dissolved in 30% MeOH:THF (10 mL) and water (5 mL) was heated at reflux for 2 hours. An additional quantity of LiOH (14 mg) was added to the solution, and refluxing was continued for an additional 2 hours. The mixture was cooled, diluted with water and 1N HCl, then extracted once with EtOAc. The organic layer was separated, washed with sat. NaCl solution, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Chromatography (silica gel, EtOAc) of the residue provided 300 mg (88%) of Example 28 as a colorless solid. ¹H NMR (DMSO-d₆) δ : 12.80 (s, 1H), 11.05 (s, 1H), 8.57 (t, 5Hz, 1H), 7.9-6.73 (m, 12H), 6.0 (d, J=2 Hz, 2H), 4.95 (ABq, J=5, 16 Hz, 2H), 4.45 (d, J=13 Hz, 1H), 3.3 (dt, J=5, 16 Hz, 1H), 2.9 (dt, J=5, 16 Hz, 1H), 2.75 (dd, J=5, 16 Hz, 1H); MS ES+m/e 486.1 (p+1) ES-m/e 484.2 (p-1); Anal. Calcd. for C₂₇H₂₃N₃O₄S: C, 66.78; H, 4.77; N, 8.65. Found: C, 66.81; H, 4.85; N, 8.38.

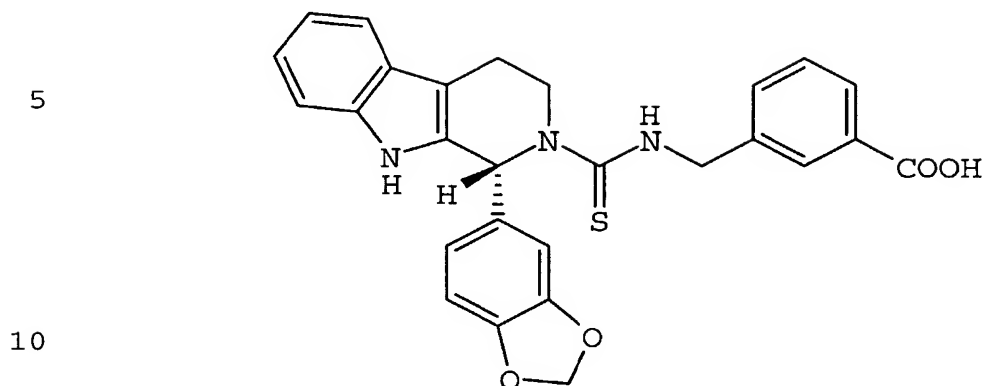
10

15

20

25

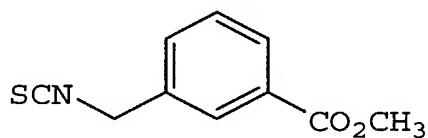
- 68 -

Example 29

15 Example 29 was prepared by the following synthetic sequence.

Preparation of 3-isothiocyanatomethylbenzoic acid methyl ester (Intermediate 8)

20

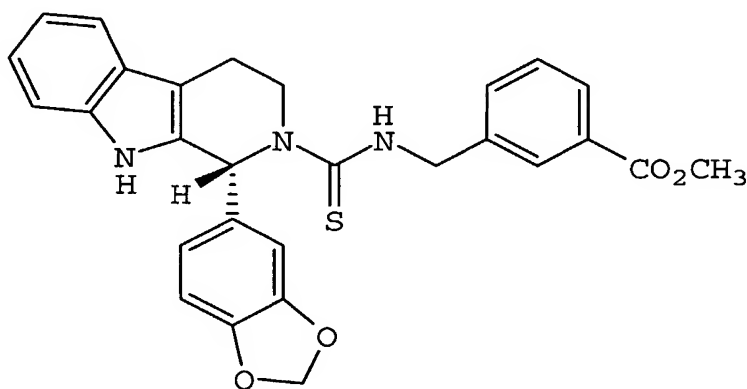


25

30 Intermediate 8 was prepared by the same procedure used to prepare Intermediate 7 using 3-bromomethylbenzoic acid methyl ester. The crude Intermediate 8 was used without further purification.

- 69 -

Preparation of (1R)-3-{[(1-benzo[1,3]dioxol-5-yl-
1,3,4,9-tetrahydro- β -carboline-2-carbthioyl)-
amino]methyl}benzoic acid methyl ester
(Intermediate 9)



Intermediate 9 was prepared by the same procedure used to prepare Intermediate 7. Purification of the crude material by chromatography (silica gel, 30% EtOAc:hexanes) gave 800 mg (47%) of Intermediate 8 as a foam. ^1H NMR (DMSO- d_6) δ : 11.05 (s, 1H), 8.6 (t, $J=5$ Hz, 1H), 7.9-6.7 (m, 12H), 6.0 (d, $J=2.5$ Hz, 2H), 4.9 (ABq, $J=5, 15$ Hz, 2H), 4.42 (d, $J=15$ Hz, 1H), 3.8 (s, 3H), 3.3 (dt, $J=3, 15$ Hz, 1H), 2.9 (dt, $J=3, 15$ Hz, 1H), 2.77 (dd, $J=3, 15$ Hz, 1H); MS ES+m/e 500.1 (p+1), ES-m/e 498.2 (p-1).

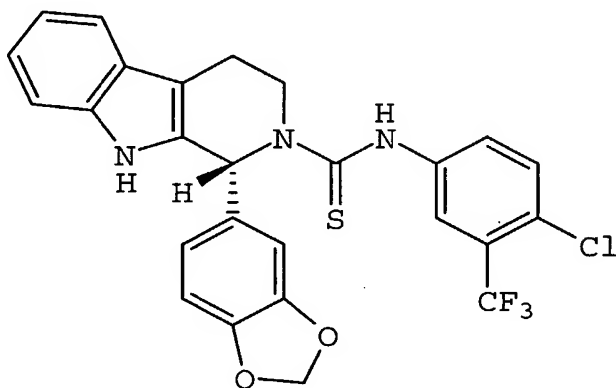
Preparation of (1R)-3-{[(1-benzo[1,3]dioxol-5-yl-
1,3,4,9-tetrahydro- β -carboline-2-carbthioyl)-
amino]methyl}benzoic acid (Example 29)

Example 29 was prepared by the same procedure used to prepare Example 28. The crude material was recrystallized from EtOAc to give 180 mg (23%) of Example 29 as a colorless solid: mp

- 70 -

218-220°C. ^1H NMR (DMSO- d_6) δ : 11.05 (s, 1H), 8.6 (t, J=5 Hz, 1H), 7.9-6.7 (m, 12H), 6.0 (d, J=2.5 Hz, 2H), 4.9 (ABq, J=5, 15 Hz, 2H), 4.42 (d, J=15 Hz, 1H), 3.3 (dt, J=3, 15 Hz, 1H), 2.9 (dt, J=3, 15 Hz, 1H), 2.77 (dd, J=3, 15 Hz, 1H); MS ES+m/e 500.1 (p+1), ES-m/e 498.2 (p-1); MS ES+m/e 486.1 (p+1), ES-m/e 484.2 (p-1); IR (KBr, cm^{-1}): 1683, 1538, 1484; Anal. Calcd. for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$: C, 66.79; H, 4.77; N, 8.65. Found: C, 66.39; H, 4.62; N, 8.41.

Example 30

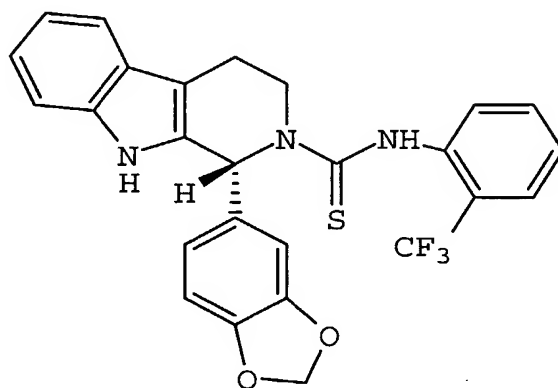


Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid (4-chloro-3-trifluoromethylphenyl)amide (Example 30)

Addition of 4-chloro-3-trifluoromethyl-phenyl isothiocyanate to the (R)-isomer of compound (III) provided Example 30 in 79% yield. ¹H NMR (DMSO-d₆) δ: 11.1 (s, 1H), 9.74 (s, 1H), 7.90-7.86 (m, 1H), 7.82 (s, 1H), 7.76-7.69 (m, 1H), 7.50 (d, J=7 Hz, 1H), 7.32 (d, J=8 Hz, 1H), 7.13-6.98 (m,

- 71 -

4H), 6.90 (d, J=8 Hz, 1H), 6.79 (d, J=8 Hz, 1H),
6.02, 6.01 (overlapping s, 2H), 4.62 (broad d, J=12
Hz, 1H), 3.41 (m, 1H), 3.07 (m, 1H), 2.84 (dd, J=3,
15 Hz, 1H); MS ES+m/e 530 (p+1), ES-m/e 528 (p-1);
5 IR (KBr, cm⁻¹): 3462, 1503, 1488, 1446; 82% ee.

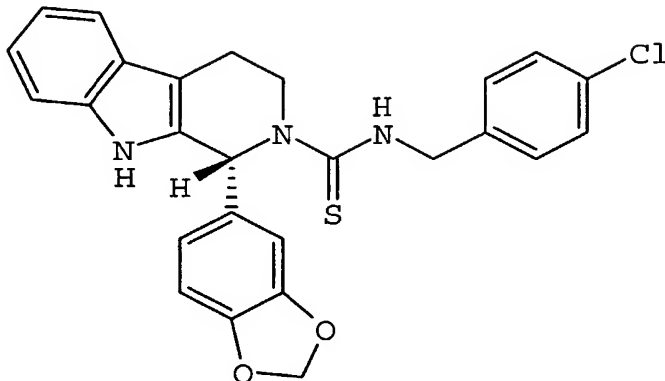
Example 31

20 Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-
tetrahydro-β-carboline-2-carbothioic acid (2-
trifluoromethylphenyl) amide
25 (Example 31)

Addition of 1-trifluoromethylphenyl
isothiocyanate to the (R)-isomer of compound (III)
provided Example 31 in 70% yield. ¹H NMR (DMSO-d₆)
δ: 10.9 (s, 1H), 9.3 (s, 1H), 7.78 (s, 1H), 7.65-
30 7.58 (m, 2H), 7.45-7.43 (m, 3H), 7.29 (d, J=8 Hz,
1H), 7.10-6.95 (m, 3H), 6.8-6.73 (m, 2H), 5.94-5.93
(s, 2H), 4.56 (broad d, J=8 Hz, 1H), 3.43-3.30 (m,
1H), 3.1-2.95 (m, 1H), 2.77 (d, J=3, 15 Hz, 1H); MS
ES+m/e 496 (p+1), ES-m/e 494 (p-1); IR (KBr, cm⁻¹):
35 1513, 1503, 1488; Anal. Calcd. for C₂₆H₂₀F₃N₃O₂S: C,

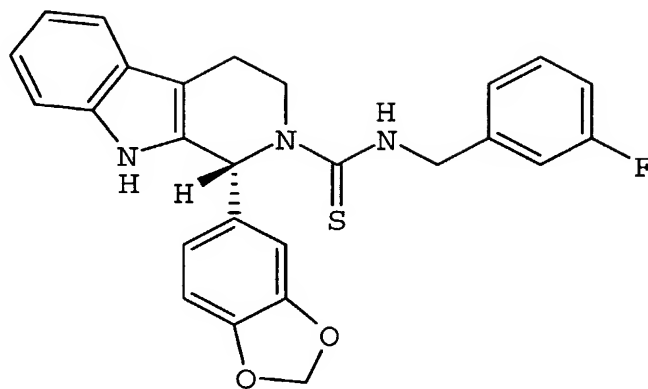
- 72 -

63.02; H, 4.06; N, 8.47. Found: C, 62.94; H, 3.80; N, 8.39; 100% ee.

Example 32**Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 4-chlorobenzylamide (Example 32)**

Addition of 4-chloromethylbenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 32 in 79% yield. ^1H NMR (CDCl_3) δ : 7.78 (s, 1H), 7.57 (s, 1H), 7.38 (d, $J=8$ Hz, 1H), 7.22-7.00 (m, 9H), 6.77 (d, $J=8$ Hz, 1H), 6.61 (d, $J=8$ Hz, 1H), 5.84 (s, 2H), 4.85 (dd, $J=5, 14$ Hz, 1H), 4.75 (dd, $J=5, 14$ Hz, 1H), 4.07 (dd, $J=4, 14$ Hz, 1H), 3.50-3.37 (m, 1H), 2.80-2.75 (m, 1H), 2.67 (dd, $J=3, 15$ Hz, 1H); MS ES+m/e 476 (p+1), ES-m/e 474 (p-1); IR (KBr, cm^{-1}): 1520, 1503, 1489; 53% ee.

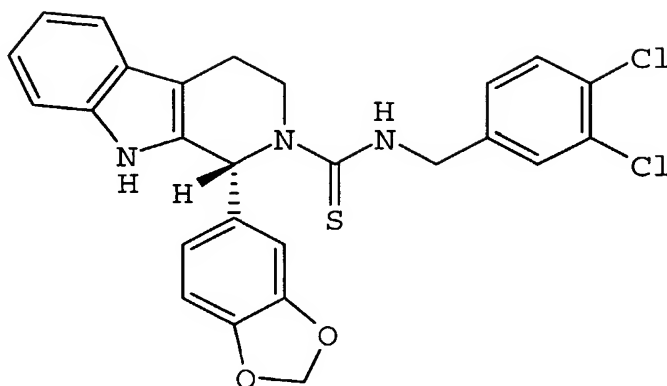
- 73 -

Example 33

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 3-fluorobenzylamide (Example 33)

Addition of 3-fluorobenzyl isothiocyanate to the (R)-isomer of compound (III) provide Example 33 in 100% yield. mp 179-181°C. ^1H NMR (DMSO- d_6) δ : 11.08 (s, 1H), 8.53 (s, 1H), 7.78 (s, 1H), 7.48 (d, J=7 Hz, 1H), 7.38-7.31 (m, 2H), 7.15-6.99 (m, 7H), 6.87 (d, J=8 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 6.01, 6.00 (overlapping s, 2H), 4.96 (dd, J=4, 15 Hz, 1H), 4.75 (dd, J=4, 15 Hz, 1H), 4.46 (broad d, J=12 Hz, 1H), 3.35-3.25 (m, 1H), 2.96-2.85 (m, 1H), 2.70 (dd, J=3, 15 Hz, 1H); MS ES+m/e 460 (p+1), ES-m/e 458 (p-1); 77% ee.

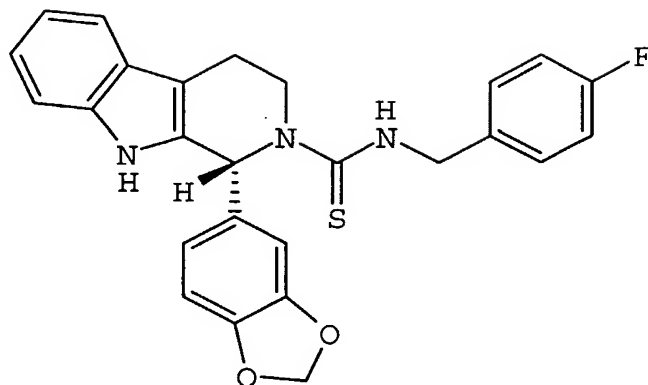
- 74 -

Example 34

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carbothioic acid 3,4-dichlorobenzylamide (Example 34)

Addition of 3,4-dichlorobenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 34 in 94% yield. ¹H NMR (DMSO-d₆) δ: 11.10 (s, 1H), 8.58 (t, J=5 Hz, 1H), 7.74 (s, 1H), 7.52-7.48 (m, 2H), 7.47 (d, J=7 Hz, 1H), 7.30 (t, J=8 Hz, 2H), 7.08 (t, J=7 Hz, 1H), 7.05-6.95 (m, 2H), 6.86 (d, J=8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 6.01, 6.0 (overlapping s, 2H), 4.90 (dd, J=5, 15 Hz, 1H), 4.80 (dd, J=5, 15 Hz, 1H), 4.45 (broad d, J=14 Hz, 1H), 3.40-3.25 (m, 1H), 3.00-2.82 (m, 1H), 2.77 (dd, J=4, 15 Hz, 1H); MS ES+m/e 510 (p+1), ES-m/e 508 (p-1); IR (KBr, cm⁻¹): 1520, 1503, 1488; Anal. Calcd. for C₂₆H₂₁Cl₂N₃O₂S: C, 61.17; H, 4.14; N, 8.23. Found: C, 61.33; H, 4.18; N, 8.29; 30% ee.

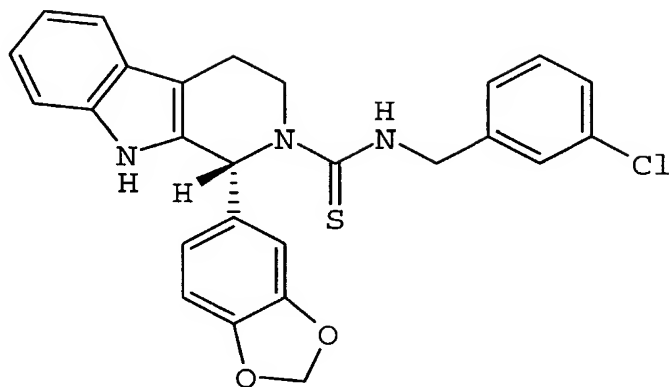
- 75 -

Example 35

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-β-carboline-2-carbothioic acid 4-fluorobenzylamide (Example 35)

Addition of 4-fluorobenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 35 in 60% yield. mp 137-139°C. ¹H NMR (DMSO-d₆) δ: 11.08 (s, 1H), 8.54 (t, J=5 Hz, 1H), 7.78 (s, 1H), 7.47 (d, J=7 Hz, 1H), 7.37-7.30 (m, 3H), 7.16-6.98 (m, 5H), 6.87 (d, 7 Hz, 1H), 6.76 (d, J=8 Hz, 1H), 6.01, 6.0 (overlapping s, 2H), 4.90 (dd, J=5, 15 Hz, 1H), 4.80 (dd, J=5, 15 Hz, 1H), 4.43 (broad d, J=12 Hz, 1H), 3.40-3.25 (m, 1H), 3.00-2.82 (m, 1H), 2.77 (dd, J=4, 15 Hz, 1H), MS ES+m/e 460 (p+1), ES-m/e 458 (p-1); 9% ee.

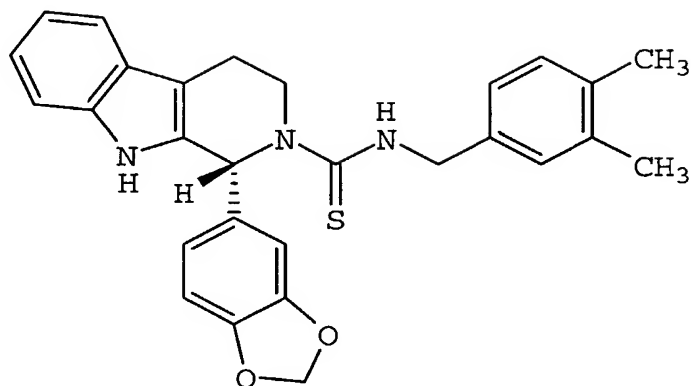
- 76 -

Example 36

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 3-chlorobenzylamide (Example 36)

Addition of 3-chlorobenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 36 in 95% yield. mp 189-191°C. ¹H NMR (DMSO-d₆) δ : 11.08 (s, 1H), 8.56 (t, J=5 Hz, 1H), 7.78 (s, 1H), 7.48 (d, J=7 Hz, 1H), 7.36-7.22 (m, 6H), 7.12-6.99 (m, 3H), 6.87 (d, J=8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 6.01, 6.00 (overlapping s, 2H), 4.93 (dd, J=5, 15 Hz, 1H), 4.81 (dd, J=5, 15 Hz, 1H), 4.45 (broad d, J=12 Hz, 1H), 3.36-3.25 (m, 1H), 2.96-2.85 (m, 1H), 2.77 (dd, J=3, 15 Hz, 1H); MS ES+m/e 477 (p+1), ES-m/e 475 (p-1); Anal. Calcd. for C₂₆H₂₂ClN₃O₂S: C, 65.60; H, 4.65; N, 8.82. Found: C, 65.75; H, 4.61; N, 8.71; 17% ee.

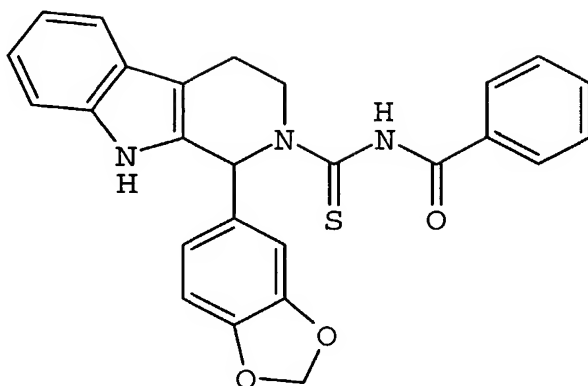
- 77 -

Example 37

Preparation of (1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 3,4-dimethylbenzylamide (Example 37)

Addition of 3,4-dimethylbenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 37 in 100% yield. mp 138-142°C. ^1H NMR (DMSO- d_6) δ : 11.10 (s, 1H), 8.45 (t, $J=5$ Hz, 0.7H), 8.31 (t, $J=5$ Hz, 0.3 H), 7.80 (s, 1H), 7.47 (d, $J=7$ Hz, 1H), 7.31 (d, $J=8$ Hz, 1H), 7.12-6.99 (m, 8H), 6.86 (d, $J=8$ Hz, 1H), 6.75 (d, $J=8$ Hz, 1H), 6.01, 6.0 (overlapping s 2H), 4.92 (dd, $J=5, 15$ Hz, 1H), 4.65 (dd, $J=5, 15$ Hz, 1H), 4.46 (broad d, $J=12$ Hz, 1H), 3.32-3.22 (m, 1H), 2.93-2.84 (m, 1H), 2.74 (dd, $J=3, 15$ Hz, 1H), 2.18 (s, 6H); MS ES+m/e 470 (p+1), ES-m/e 468 (p-1); Anal. Calcd. for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 76.61; H, 5.97; N, 8.94. Found: C, 71.73; H, 5.80; N, 8.99.

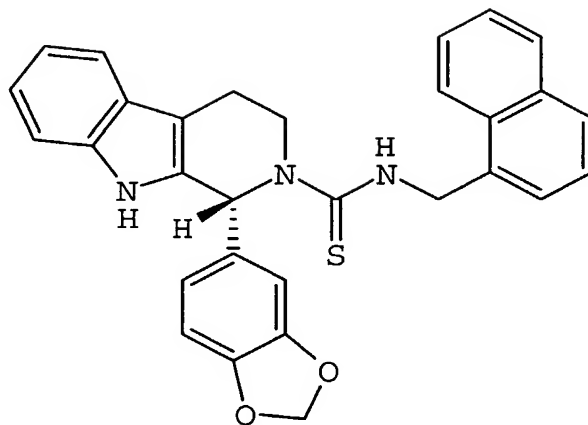
- 78 -

Example 38

Preparation of N-[(1-(2H-benzo[d][1,3-dioxolan-5-yl)(1,2,3,4-tetrahydrobeta-carbolin-2-yl)thioxomethyl]benzamide (Example 38)

The addition of benzoyl isothiocyanate to the (R)-isomer of compound (III) provided Example 38 in 88% yield. mp 207-208°C. ¹NMR (DMSO-d₆) δ: 7.96 (d, J=7.3 Hz, 2 H), 7.85 (s, 1H), 7.46-7.65 (m, 2H), 7.34 (d, J=8.4 Hz, 1H), 7.04-7.15 (m, 5H); 6.8-7.0 (m, 2H), 6.04 (s, 2H), 4.32 (dd, J=4.1, 8.7 Hz, 1H), 3.40-3.49 (m, 1H), 2.90-3.08 (m, 1H), 2.82 (dd, J=1.4, 15.7 Hz, 1H); MS ES+m/e 456.3 (p+1), ES-m/e 454.1 (p-1).

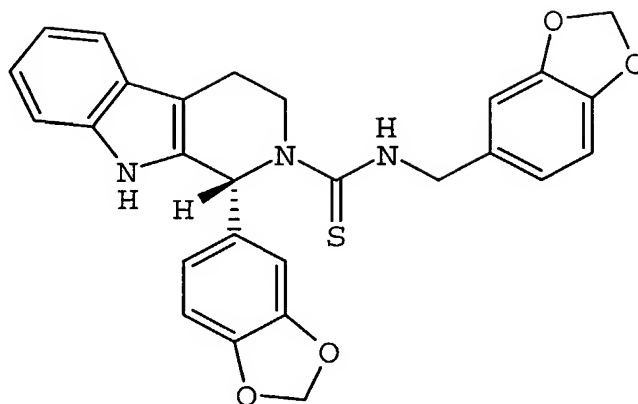
- 79 -

Example 39

Preparation of (1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid (naphthalen-1-yl-methyl)amide (Example 39)

Addition of α -naphthylmethyl isothiocyanate to the (R)-isomer of compound (III) provided Example 39 in 81% yield. mp 111-113°C. ^1H NMR (DMSO- d_6) δ : 2.75 (dd, $J=4, 15$ Hz, 1H), 2.92 (dt, $J=4, 12$ Hz, 1H), 3.27 (dt, $J=4, 12$ Hz, 2H), 4.5 (dd, $J=4, 12$ Hz, 1H), 4.82 (dq, $J=4, 22$ Hz, 2H), 6.05 (s, 2H), 6.7-8.5 (m, 16H), 8.5 (t, $J=4$ Hz, 1H), 11.08 (s, 1H); MS ES+m/e 492.2 (p+1), ES-m/e 490.3 (p-1), MS FD m/e 491.2.

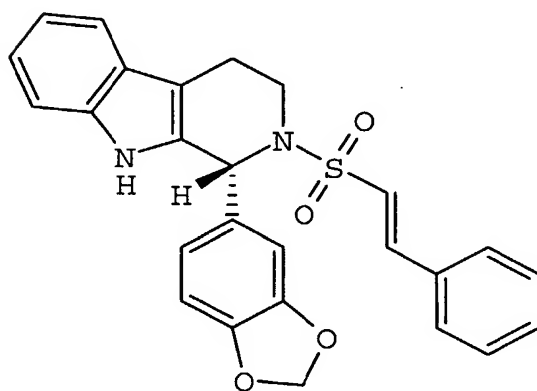
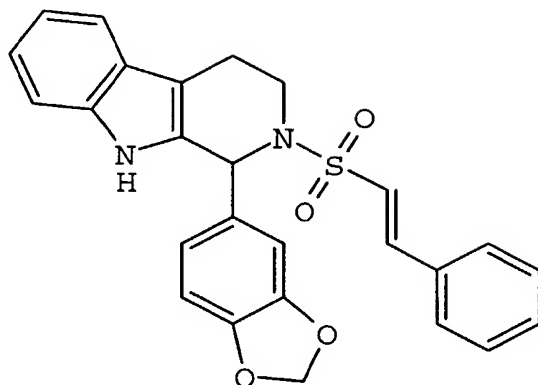
- 80 -

Example 40

Preparation of (1R)-1-benzo-[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid (benzo[1,3]dioxol-5-yl-methyl)amide (Example 40)

The addition of 3,4-methylenedioxybenzyl isothiocyanate to the (R)-isomer of compound (III) provided Example 40 in 38% yield. mp 97-100°C. ^1H NMR (DMSO- d_6) δ : 2.7 (dd, $J=4$, 15 Hz, 1H), 2.83 (dt, $J=4$, 12 Hz, 1H), 3.25 (dt, $J=4$, 12 Hz, 1H), 4.35 (dd, $J=4$, 12 Hz, 1H), 4.75 (dq, $J=4$, 18 Hz, 2H), 5.95 (s, 2H), 6.02 (s, 2H), 6.6-7.7 (m, 12H), 8.42 (t, $J=4$ Hz, 1H), 11.04 (s, 1H); MS ES+m/e 486.2 (p+1), ES-m/e 484.2 (p-1).

- 81 -

Examples 41a and 41b

Preparation of 1-benzo[1,3]dioxol-5-yl-2-(2-phenylethenesulfonyl)-2,3,4,9-tetrahydro-1H- β -carboline (Example 41a)

2-Phenylethenesulfonyl chloride was added to compound (III) to provide Example 41a in 60% yield. mp 191-192°C. ^1H NMR (DMSO- d_6) δ : 10.85 (s, 1H), 7.46-7.22 (s, 9H), 7.08-6.96 (m, 3H), 6.87 (d, J=7 Hz, 1H), 6.79 (s, 1H), 6.68 (dd, J=1.4 Hz, 8 Hz, 1H), 5.98 (s, 2H), 3.92 (dd, J=5, 14 Hz, 1H), 3.40-

- 82 -

3.20 (m, 1H), 2.97-2.86 (m, 1H), 2.78 (dd, J=4, 15 Hz, 1H); MS ES+m/e 459 (p+1), ES-m/e 457 (p-1); IR (KBr, cm⁻¹): 3462, 1503, 1488, 1446.

5 **Preparation of (1R)-1-benzo[1,3]dioxol-5-yl-2-(2-phenylethanesulfonyl)-2,3,4,9-tetrahydro-1H- β -carboline (Example 41b)**

10 Addition of 2-phenylethanesulfonyl chloride to the (R)-isomer of compound (III) provided Example 41b in 44% yield. mp 193-194°C. ¹H NMR (DMSO-d₆) δ : 10.85 (s, 1H), 7.46-7.22 (s, 9H), 7.08-6.96 (m, 3H), 6.87 (d, J=7 Hz, 1H), 6.79 (s, 1H), 6.68 (dd, J=1.4 Hz, 8 Hz, 1H), 5.98 (s, 2H), 3.92 (dd, J=5, 14 Hz, 1H), 3.40-3.20 (m, 1H), 2.97-2.86 (m, 1H), 2.78 (dd, J=4, 15 Hz, 1H); MS ES+m/e 459 (p+1), ES-m/e 457 (p-1); IR (KBr, cm⁻¹): 3462, 1503, 1488, 1446; Anal. Calcd. for C₂₆H₂₂N₂O₄S: C, 68.10; H, 4.83; N, 6.10. Found: C, 67.77; H, 4.84; N, 6.09; 92% ee.

Compounds of the present invention can be formulated into tablets for oral administration. For example, a compound of formula (I) can be formed into a dispersion with a polymeric carrier by the coprecipitation method set forth in Butler U.S. Patent No. 5,985,326 incorporated herein by reference. The coprecipitated dispersion then can be blended with excipients, then pressed into tablets, which optionally are film-coated.

The compounds of structural formula (I) were tested for an ability to inhibit PDE5. The ability of a compound to inhibit PDE5 activity is

- 83 -

related to the IC_{50} value for the compound, i.e., the concentration of inhibitor required for 50% inhibition of enzyme activity. The IC_{50} value for compounds of structural formula (I) were determined using recombinant human PDE5.

The compounds of the present invention typically exhibit an IC_{50} value against recombinant human PDE5 of less than about 50 μM , and preferably less than about 25 μM , and more preferably less than about 15 μM . The compounds of the present invention typically exhibit an IC_{50} value against recombinant human PDE5 of less than about 1 μM , and often less than about 0.05 μM . To achieve the full advantage of the present invention, a present PDE5 inhibitor has an IC_{50} of about 0.1 nM to about 15 μM .

The production of recombinant human PDEs and the IC_{50} determinations can be accomplished by well-known methods in the art. Exemplary methods are described as follows:

EXPRESSION OF HUMAN PDEs

Expression in *Saccharomyces cerevisiae* (Yeast)

Recombinant production of human PDE1B, PDE2, PDE4A, PDE4B, PDE4C, PDE4D, PDE5, and PDE7 was carried out similarly to that described in Example 7 of U.S. Patent No. 5,702,936, incorporated herein by reference, except that the yeast transformation vector employed, which is derived from the basic ADH2 plasmid described in Price et al., *Methods in Enzymology*, 185, pp. 308-318 (1990), incorporated yeast ADH2 promoter and terminator sequences and the

- 84 -

Saccharomyces cerevisiae host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Trans-
5 formed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium-containing glycerol was added to a final concentration of 2X YET/3% glycerol. Approxi-
10 mately 24 hr later, cells were harvested, washed, and stored at -70°C.

HUMAN PHOSPHODIESTERASE PREPARATIONS

Phosphodiesterase Activity Determinations

15 Phosphodiesterase activity of the preparations was determined as follows. PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al. (1996).
20 In this assay, PDE activity converts [32P]cAMP or [32P]cGMP to the corresponding [32P]5'-AMP or [32P]5'-GMP in proportion to the amount of PDE activity present. The [32P]5'-AMP or [32P]5'-GMP then was quantitatively converted to free [32P]phosphate
25 and unlabeled adenosine or guanosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [32P]phosphate liberated is proportional to enzyme activity. The assay was performed at 30°C in a 100 µL reaction mixture containing (final concentra-
30 tions) 40 mM Tris HCl (pH 8.0), 1 µM ZnSO₄, 5 mM MgCl₂, and 0.1 mg/mL bovine serum albumin (BSA). PDE enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay condi-

- 85 -

tions). The assay was initiated by addition of substrate (1 mM [32P]cAMP or cGMP), and the mixture was incubated for 12 minutes. Seventy-five (75) μ g of *Crotalus atrox* venom then was added, and the incubation was continued for 3 minutes (15 minutes total). The reaction was stopped by addition of 200 μ L of activated charcoal (25 mg/mL suspension in 0.1 M NaH_2PO_4 , pH 4). After centrifugation (750 X g for 3 minutes) to sediment the charcoal, a sample of the supernatant was taken for radioactivity determination in a scintillation counter and the PDE activity was calculated.

Purification of PDE5 from *S. cerevisiae*

Cell pellets (29 g) were thawed on ice with an equal volume of Lysis Buffer (25 mM Tris HCl, pH 8, 5 mM MgCl_2 , 0.25 mM DTT, 1 mM benzamidine, and 10 μ M ZnSO_4). Cells were lysed in a Microfluidizer[®] (Microfluidics Corp.) using nitrogen at 20,000 psi. The lysate was centrifuged and filtered through 0.45 μ m disposable filters. The filtrate was applied to a 150 mL column of Q SEPHAROSE[®] Fast-Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM MgCl_2 , 0.25 mM DTT, 10 μ M ZnSO_4) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A. Active fractions from the linear gradient were applied to a 180 mL hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM MgCl_2 , 0.25 mM DTT, 10 μ M ZnSO_4 , and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer

- 86 -

B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM DTT, and 10 μ M ZnSO₄). The pool was applied to a 140 mL column of SEPHACRYL[®] S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20°C.

The resultant preparations were about 85% pure by SDS-PAGE. These preparations had specific activities of about 3 μ mol cGMP hydrolyzed per minute per milligram protein.

Inhibitory Effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al., *Biochim. Biophys. Acta*, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 μ g/ml 5'-Nucleotidase, 1 mM EGTA, and 0.15 μ M 8-[H³]-cGMP. Unless otherwise indicated, the enzyme used was a human recombinant PDE5 (ICOS Corp., Bothell, Washington).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC₅₀ values for the compounds examined were determined from concentration-response curves typically using concentrations ranging from 10 nM to 10 μ M. Tests against other PDE enzymes using

- 87 -

standard methodology showed that compounds of the invention are selective for the cGMP-specific PDE enzyme.

5 Biological Data

The compounds according to the present invention were typically found to exhibit an IC₅₀ value of less than 500 nM (i.e., 0.5 μ M). *In vitro* test data for representative compounds of the inven-
10 tion is given in the following table:

Table 1: <i>In vitro</i> Results	
Example	PDE5 IC ₅₀ (μ M)
1	0.167
2a	0.051
2b	0.040
4	0.8
5	0.4
6	0.4
7	0.85
10	0.013
12	0.049
15a	0.017
15b	0.009
16	0.209
17	0.029
19	0.001
20	0.001

- 88 -

Table 1: *In vitro* Results

Example	PDE5 IC ₅₀ (μ M)
21	0.18
22	0.15
23	0.44
24	0.177
25	0.126
26	0.040
27	0.196
28	0.036
29	0.469
30	0.083
31	0.518
32	0.051
33	0.075
34	0.512
35	0.122
36	0.494
37	0.030
38	0.379
39	0.119
40	0.056
41a	0.675
41b	0.413

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope

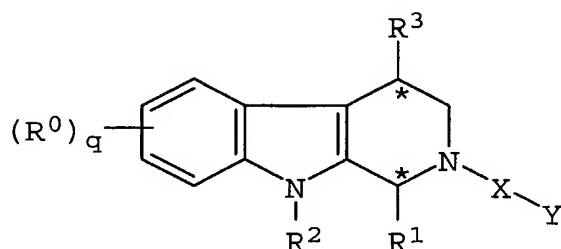
- 89 -

thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

- 90 -

WHAT IS CLAIMED IS:

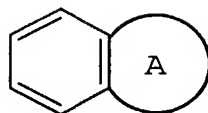
1. A compound having a formula



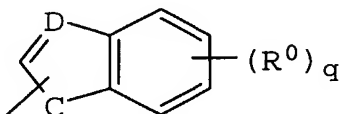
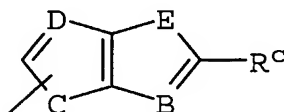
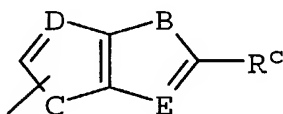
wherein R^0 , independently, is selected from the group consisting of halo, C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, C_{3-8} cycloalkylQ, $C(=O)R^a$, $OC(=O)R^a$, $C(=O)OR^a$, C_{1-4} alkylene NR^aR^b , C_{1-4} alkyleneHet, C_{1-4} alkylene $C(=O)OR^a$, $C(=O)NR^aSO_2R^c$, $C(=O)C_{1-4}$ alkyleneHet, $C(=O)NR^aR^b$, $C(=O)NR^aR^c$, $C(=O)NR^aC_{1-4}$ alkylene OR^b , $C(=O)NR^aC_{1-4}$ alkyleneHet, OR^a , OC_{1-4} alkylene $C(=O)OR^a$, OC_{1-4} alkylene NR^aR^b , OC_{1-4} alkyleneHet, OC_{1-4} alkylene OR^a , OC_{1-4} alkylene $NR^aC(=O)OR^b$, NR^aR^b , NR^aC_{1-4} alkylene NR^aR^b , $NR^aC(=O)R^b$, $NR^aC(=O)NR^aR^b$, $N(SO_2C_{1-4}alkyl)_2$, $NR^a(SO_2C_{1-4}alkyl)$, nitro, trifluoromethyl, trifluoromethoxy, cyano, $SO_2NR^aR^b$, SO_2R^a , SOR^a , SR^a , and OSO_2CF_3 ;

R^1 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, an optionally substituted C_{3-8} cycloalkyl ring, an optionally substituted C_{3-8} heterocycloalkyl ring, an optionally substituted bicyclic ring

- 91 -

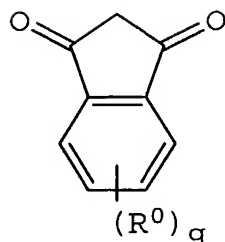


wherein the fused ring A is a 5- or 6-membered ring, saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one to three heteroatoms selected from oxygen, sulfur, and nitrogen, hydrogen, C_{1-6} alkyl, aryl C_{1-3} alkyl, C_{1-3} -alkylenearyl, halo C_{1-6} alkyl, C_{1-4} alkyleneC(=O)OR^a, C_{1-4} alkyleneC(=O)NR^aR^b, C_{3-8} cycloalkenyl, C_{3-8} heterocycloalkenyl, C_{1-4} alkyleneHet, C_{1-4} alkyleneQR^a, C_{2-6} -alkenyleneQR^a, C_{1-4} alkyleneQC C_{1-4} alkyleneQR^a,



and a spiro substituent having a structure

- 92 -



;

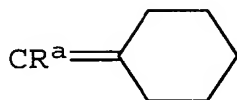
R² is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈heterocycloalkyl, C₂₋₆alkenyl, C₁₋₃alkylenearyl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, aryl, heteroaryl, C(=O)R^a, C(=O)NR^aR^b, C(=O)NR^aR^c, C(=S)NR^aR^b, C(=S)NR^aR^c, SO₂R^a, SO₂NR^aR^b, S(=O)R^a, S(=O)NR^aR^b, C(=O)NR^aC₁₋₄alkyleneOR^a, C(=O)NR^aC₁₋₄alkyleneHet, C(=O)C₁₋₄alkylenearyl, C(=O)C₁₋₄alkyleneheteroaryl, C₁₋₄alkylenearyl substituted with one or more of SO₂NR^aR^b, NR^aR^b, NR^aR^c, C(=O)OR^a, NR^aSO₂CF₃, CN, NO₂, C(=O)R^a, OR^a, C₁₋₄alkyleneNR^aR^b, and OC₁₋₄alkyleneNR^aR^b, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet, C₁₋₄alkyleneC(=O)C₁₋₄alkylenearyl, C₁₋₄alkyleneC(=O)C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneC(=O)Het, C₁₋₄alkyleneC(=O)NR^aR^b, C₁₋₄alkyleneOR^a, C₁₋₄alkyleneNR^aC(=O)R^a, C₁₋₄alkyleneOC₁₋₄alkyleneOR^a, C₁₋₄alkyleneNR^aR^b, C₁₋₄alkyleneC(=O)OR^a, and C₁₋₄alkyleneOC₁₋₄alkyleneC(=O)OR^a;

R³ is selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylC₁₋₃alkyl, C₁₋₃alkylenearyl, C₁₋₃alkyleneHet, C₃₋₈cycloalkyl, and C₃₋₈heterocycloalkyl;

X is selected from the group consisting of C(=O), C(=O)C≡C, C(=O)C(R^a)=C(R^a), C(=S), SO, SO₂, SO₂C(R^a)=CR^a, CR^aR^b, CR^a=CR^a, C(=O)NR^a, and C(=N-OR^a);

- 93 -

Y is selected from the group consisting of $(\text{CH}_2)_n\text{C}(=\text{O})\text{R}^c$, $(\text{CH}_2)_n\text{C}(=\text{O})\text{OR}^c$, $(\text{CH}_2)_n\text{aryl}$, $\text{N}(\text{R}^b)(\text{CH}_2)_n\text{R}^c$, $\text{O}(\text{CH}_2)_n\text{R}^c$, $\text{N}(\text{R}^b)\text{C}(=\text{O})\text{R}^c$, $\text{C}(\text{R}^a)=\text{NR}^c$, $\text{C}(=\text{O})\text{N}(\text{R}^a)(\text{R}^c)$, $\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^c$,



and $\text{N}(\text{R}^a)\text{SO}_2\text{R}^c$, and when X is $\text{SO}_2\text{C}(\text{R}^a)=\text{CR}^a$, Y additionally can be aryl or heteroaryl;

R^a is selected from the group consisting of hydrogen, C_{1-6} alkyl, cyano, aryl, arylC_{1-3} alkyl, C_{1-3} alkylenearyl, heteroaryl, heteroaryl C_{1-3} alkyl, and C_{1-3} alkyleneheteroaryl;

R^b is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-3} alkylene $\text{N}(\text{R}^a)_2$, aryl, arylC_{1-3} alkyl, C_{1-3} alkylenearyl, and heteroaryl;

R^c is selected from the group consisting of hydrogen, C_{1-6} alkyl, aryl, heteroaryl, arylC_{1-3} alkyl, heteroaryl C_{1-3} alkyl, C_{1-3} alkylene $\text{N}(\text{R}^a)_2$, C_{1-6} alkylenearyl, C_{1-6} alkyleneHet, haloC_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, Het, C_{1-3} alkyleneheteroaryl, C_{1-6} alkylene $\text{C}(=\text{O})\text{OR}^a$, and C_{1-3} alkylene C_{3-8} heterocycloalkyl;

or R^a and R^c are taken together to form a 5- or 6-membered ring, optionally containing at least one heteroatom;

Q is O, S, or NR^d ;

B is O, S, or NR^d ;

C is O, S, or NR^a ;

D is CR^a or N;

- 94 -

E is CR^a, C(R^a)₂, or NR^d; and

R^d is null or is selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylC₁₋₃alkyl, heteroarylC₁₋₃alkyl, C₁₋₃alkylenearyl, and C₁₋₃alkyleneheteroaryl;

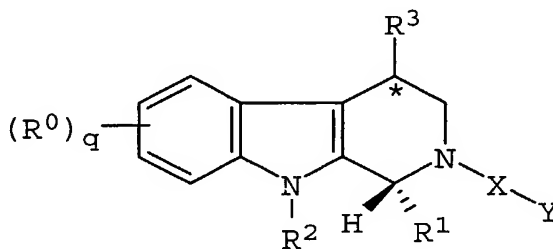
Het represents a 5- or 6-membered heterocyclic ring, saturated or partially or fully unsaturated, containing at least one heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur, and optionally substituted with C₁₋₄alkyl or C(=O)OR^a;

n is 0, 1, 2, 3, or 4;

q is 0, 1, 2, 3, or 4;

and pharmaceutically acceptable salts and solvates thereof.

2. The compound of claim 1 represented by a formula



and pharmaceutically acceptable salts and hydrates thereof.

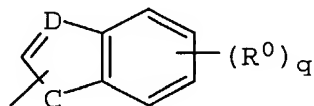
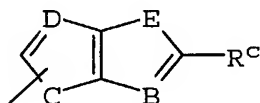
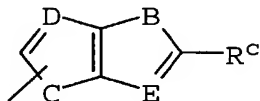
3. The compound of claim 1 wherein q is 0.

- 95 -

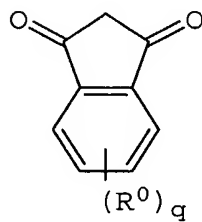
4. The compound of claim 1 wherein R^0 is selected from the group consisting of aryl, Het, OR^a , $C(=O)OR^a$, $C_{1-4}alkyleneNR^aR^b$, $OC(=O)R^a$, $C(=O)R^a$, NR^aR^b , $C_{3-8}cycloalkyl$, $C_{3-8}cycloalkylQ$, $C(=O)NR^aR^b$, and $C(=O)-NR^aR^c$.

- 96 -

5. The compound of claim 1 wherein R^1 is selected from the group consisting of C_{1-4} alkyleneQR^a, C_{1-4} alkyleneQC₁₋₄alkyleneQR^a, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{1-6} alkyl,

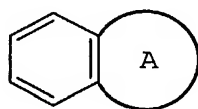


, and

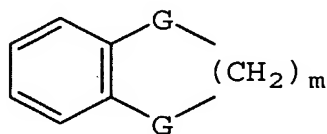


- 97 -

6. The compound of claim 1 wherein R^1 is the optionally substituted bicyclic ring system



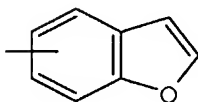
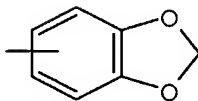
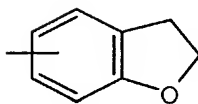
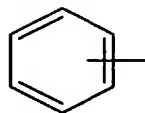
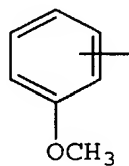
7. The compound of claim 6 wherein R^1 is



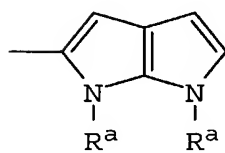
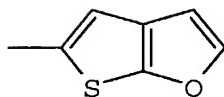
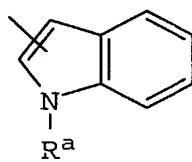
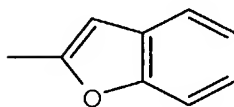
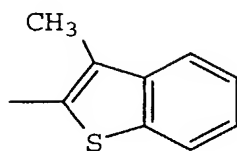
and wherein m is an integer 1 or 2, and G , independently, are $C(R^a)_2$, O, S, or NR^a .

- 98 -

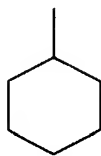
8. The compound of claim 1 wherein R¹ is selected from the group consisting of



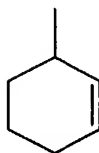
- 99 -



- 100 -

-CH₂OR^a, -CH₂OCH₂OR^a,

, and



9. The compound of claim 1 wherein the R² group is selected from the group consisting of hydrogen, aryl, heteroaryl, OR^a, NR^aR^b, NR^aR^c, C₁₋₄-alkyleneHet, C₁₋₄-alkyleneheteroaryl, C₁₋₄-alkylenearyl, C₁₋₆-alkyl, C₂₋₆-alkenyl, arylC₁₋₃-alkyl, heteroarylC₁₋₃-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl, C(=O)R^a, and SO₂NR^aR^b.

- 101 -

10. The compound of claim 9 wherein R^2 is hydrogen.

11. The compound of claim 1 wherein R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, aryl, and heteroaryl.

12. The compound of claim 1 wherein R^3 is hydrogen.

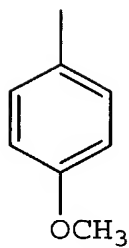
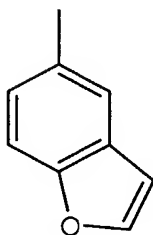
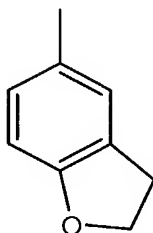
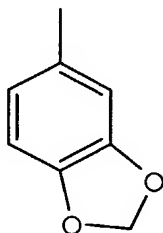
13. The compound of claim 1 wherein X is selected from the group consisting of $C=O$, $C=S$, and $SO_2CH=CH$.

14. The compound of claim 13 wherein Y is selected from the group consisting of $C(R^a)=NR^c$, $C(=O)N(R^a)(CH_2)_n(R^c)$, $N(R^b)(CH_2)_n(R^c)$, $N(R^a)C(=O)R^c$, $N(R^a)SO_2R^c$, $O(CH_2)_nR^c$, aryl when X is $SO_2CH=CH$, $(CH_2)_nC(=O)OR^a$, $(CH_2)_n$ aryl, and $(CH_2)_nC(=O)R^c$.

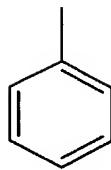
15. The compound of claim 14 wherein R^2 is hydrogen, and R^3 is hydrogen.

- 102 -

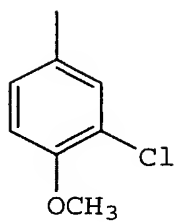
16. The compound of claim 15 wherein R¹ is selected from the group consisting of



- 103 -

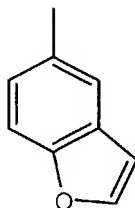
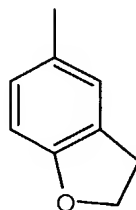
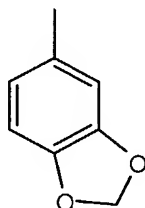


, and

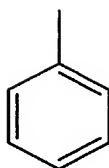
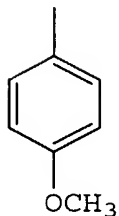


- 104 -

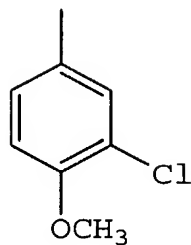
17. The compound of claim 1 wherein q is 0 or R⁰ is selected from the group consisting of halo, methyl, trifluoromethyl, and trifluoromethoxy; R¹ is selected from the group consisting of



- 105 -



, and



;

R^2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, NR^aR^c , and C_{1-4} alkyleneHet;

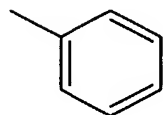
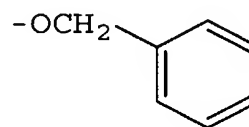
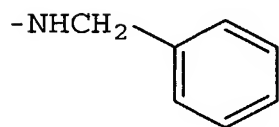
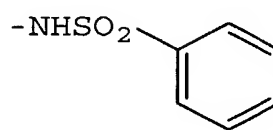
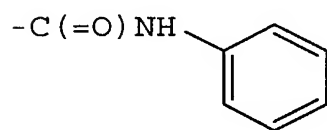
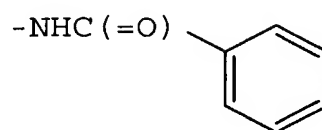
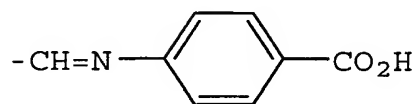
R^3 is hydrogen or C_{1-6} alkyl;

X is selected from the group consisting of $C(=O)$, $C(=S)$, and $SO_2CH=CH$;

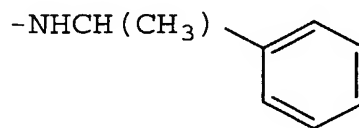
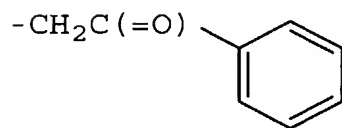
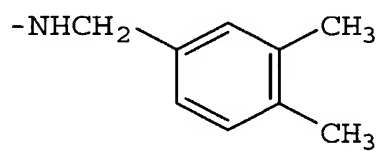
Y is selected from the group consisting of $C(R^a)=NR^c$, $C(=O)N(R^a)(R^c)$, $N(R^b)(CH_2)_n(R^c)$, $N(R^a)C(=O)-R^c$, $N(R^a)SO_2R^c$, $O(CH_2)_nR^c$, aryl when X is $SO_2CH=CH$, $(CH_2)_n$ aryl, $(CH_2)C(=O)OR^a$, and $(CH_2)_nC(=O)R^c$.

- 106 -

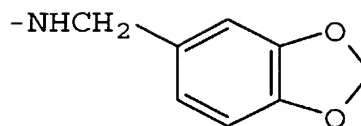
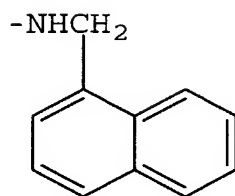
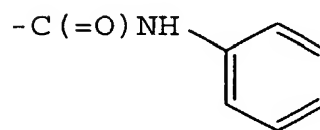
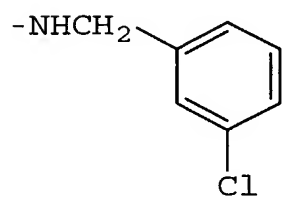
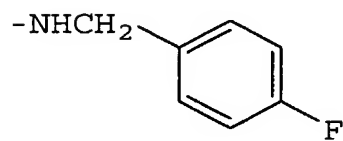
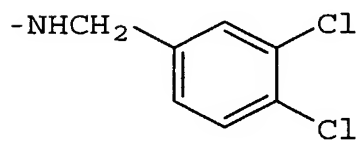
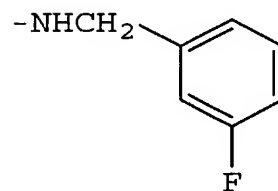
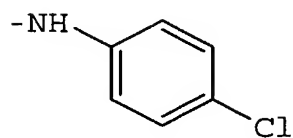
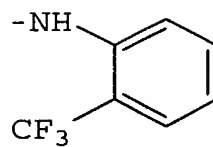
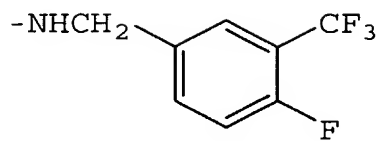
18. The compound of claim 17 wherein Y is selected from the group consisting of



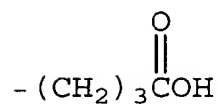
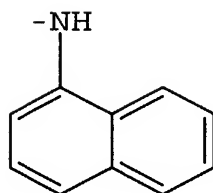
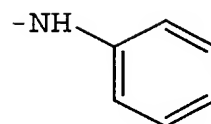
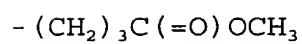
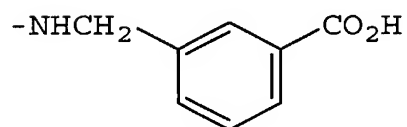
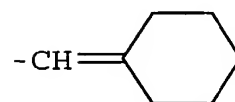
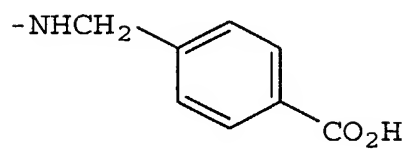
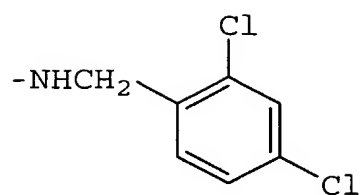
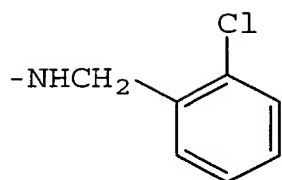
, when X
is $\text{SO}_2\text{CH}=\text{CH}$



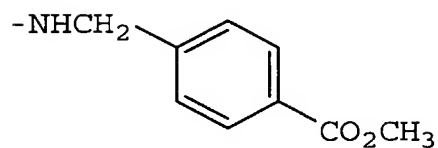
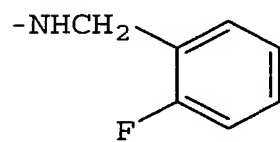
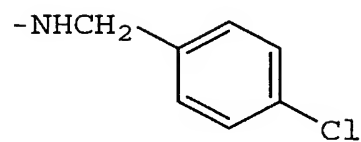
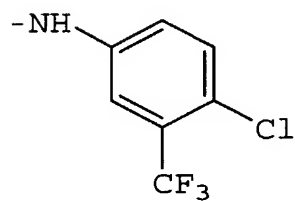
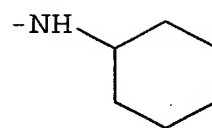
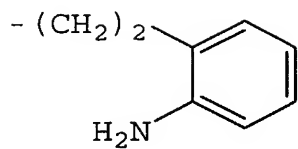
- 107 -



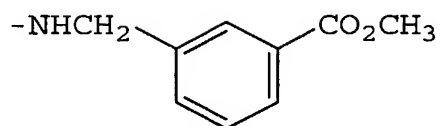
- 108 -



- 109 -



and



- 110 -

19. A compound selected from the group consisting of

(1R)-2-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-2-oxo-N-phenylacetamide

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid benzylamide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid (1S)-(phenylethyl)amide

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid (1R)-(phenylethyl)-amide

N-((1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbonyl)benzamide

1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid benzyl ester

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carboxylic acid benzyl ester

(1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carbolin-3-yl)-2-cyclohexylidene-ethanone

(1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carbolin-2-yl)-3-phenylpropane-1,3-dione

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -carboline-2-carbothioic acid 2-chlorobenzylamide

- 111 -

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 2,4-dichlorobenzylamide

(1R)-1-(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro-
 β -carboline-2-carbothioic acid ((S)-1-phenyl-
ethyl)amide

(1R)-4-{[(1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetra-
hydro- β -carboline-2-carbthioly) amino]methyl}benzoic
acid

(1R)-3-{[(1-benzo[1,3]dioxol-5-yl-1,3,4,9-
tetrahydro- β -carboline-2-carbthioly) amino]methyl}-
benzoic acid

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid (4-chloro-3-trifluoro-
methylphenyl)amide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid (2-trifluoromethyl-
phenyl)amide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 4-chlorobenzylamide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 3-fluorobenzylamide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 3,4-dichlorobenzylamide

- 112 -

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 4-fluorobenzylamide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 3-chlorobenzylamide

(1R)-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid 3,4-dimethylbenzylamide

N-[(1-(2H-benzo[d]1,3-dioxolan-5-yl)(1,2,3,4-tetra-
hydrobeta-carbolin-2-yl)thioxomethyl]benzamide

(1R)-1-benzo[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid (naphthalen-1-yl-
ethyl)amide

(1R)-1-benzo-[1,3]dioxol-5-yl-1,3,4,9-tetrahydro- β -
carboline-2-carbothioic acid (benzo[1,3]dioxol-5-yl-
methyl)amide

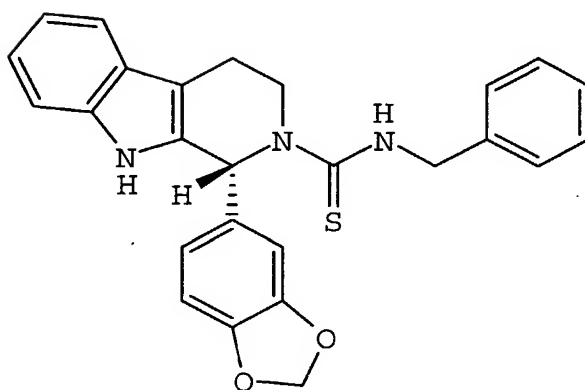
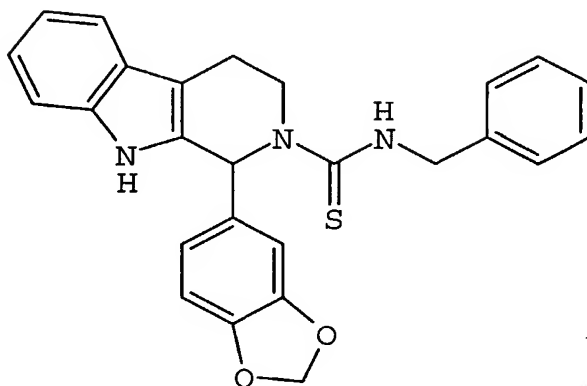
1-benzo[1,3]dioxol-5-yl-2-(2-phenylethenesulfonyl)-
2,3,4,9-tetrahydro-1H- β -carboline

(1R)-1-benzo[1,3]dioxol-5-yl-2-(2-phenylethene-
sulfonyl)-2,3,4,9-tetrahydro-1H- β -carboline

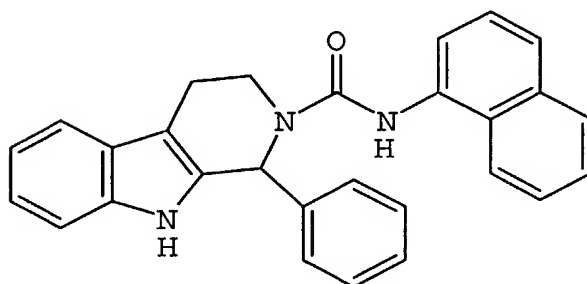
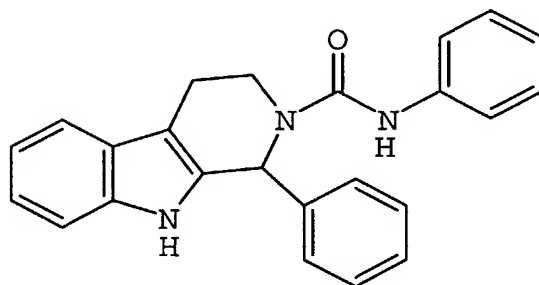
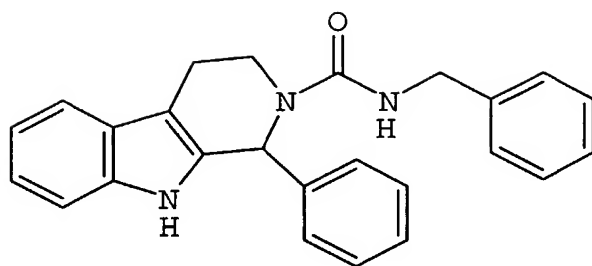
and pharmaceutically acceptable salts and
solvates thereof.

- 113 -

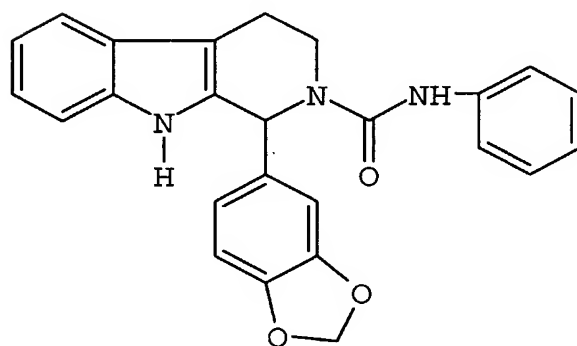
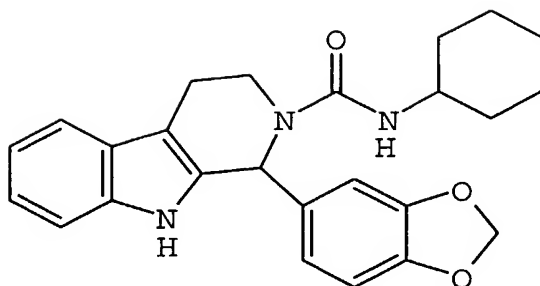
20. A compound having a formula:



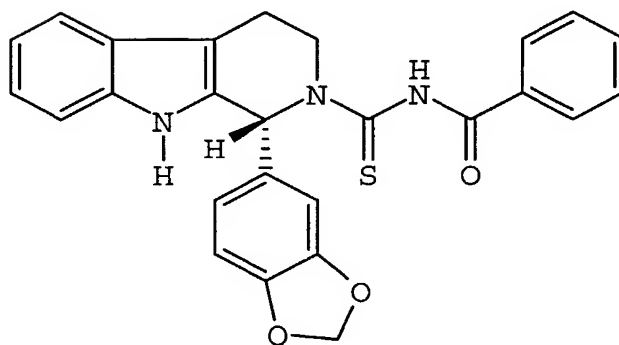
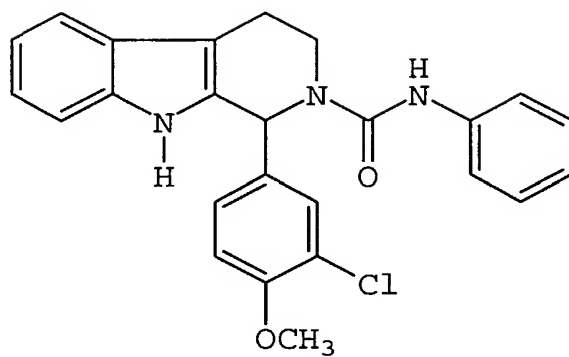
- 114 -



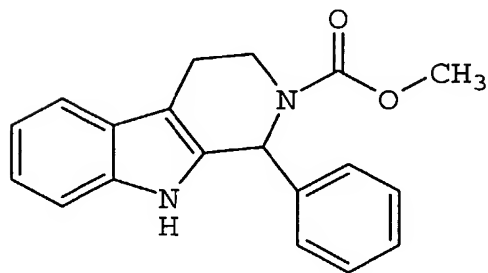
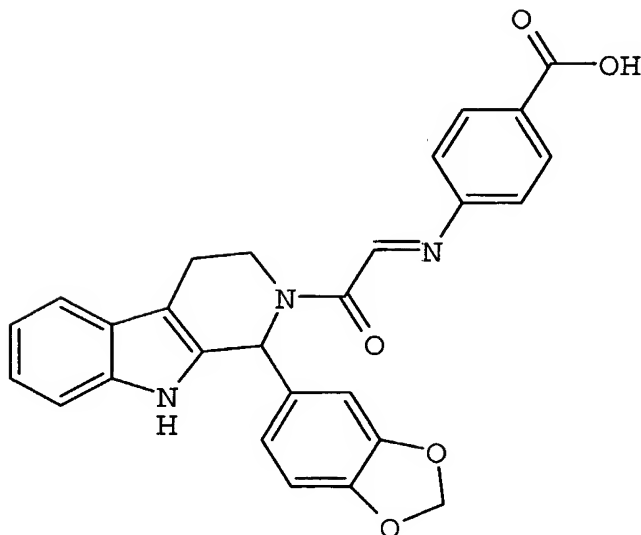
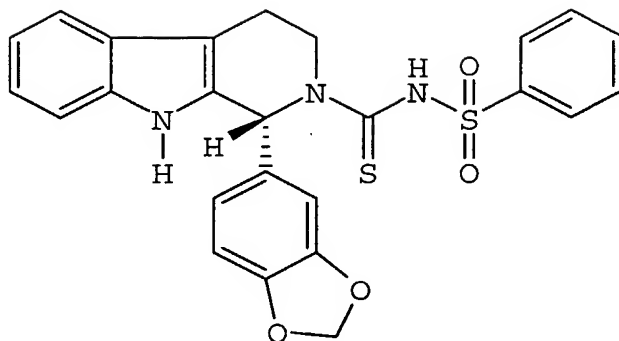
- 115 -



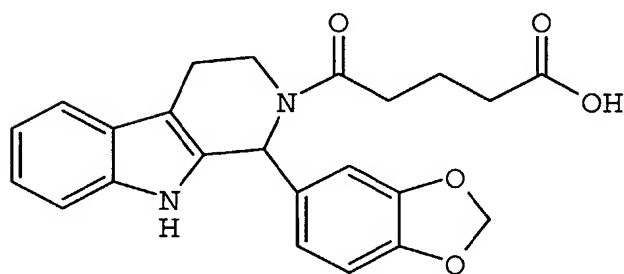
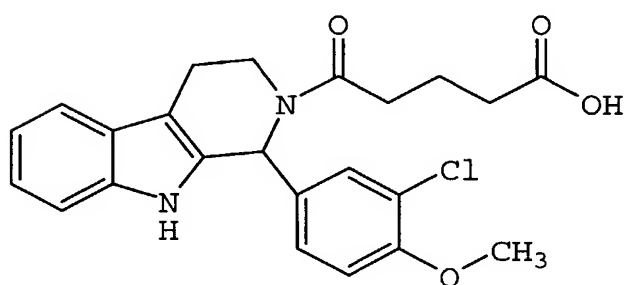
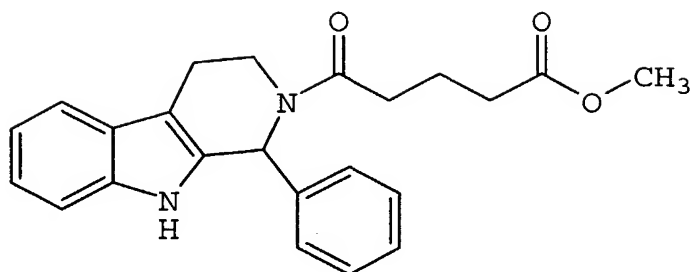
- 116 -



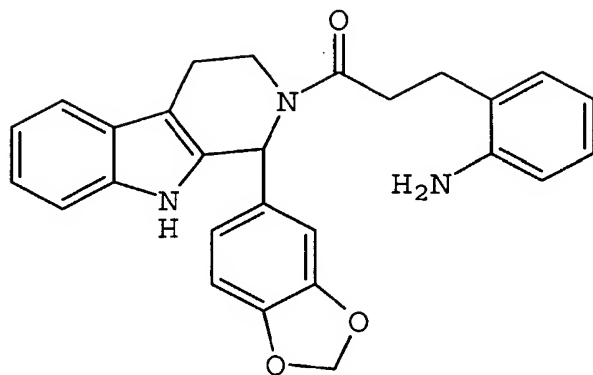
- 117 -



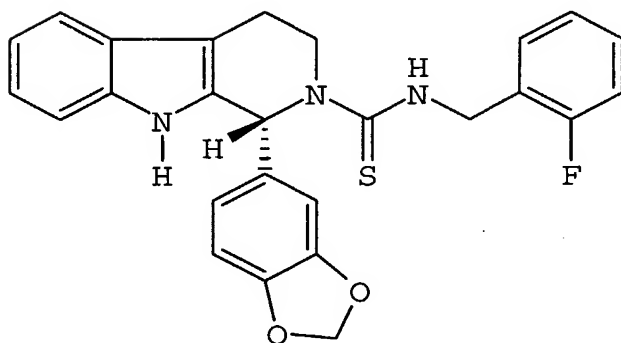
- 118 -



- 119 -



and



- 120 -

21. A pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

22. A method of treating a male or female animal in the treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit comprising treating said animal with an effective amount of a pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

23. The method of claim 22 wherein the condition is male erectile dysfunction.

24. The method of claim 23 wherein the treatment is an oral treatment.

25. The method of claim 22 wherein the condition is female arousal disorder.

26. The method of claim 25 wherein the treatment is an oral treatment.

- 121 -

27. The method of claim 22 wherein the condition is selected from the group consisting of stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, acute respiratory distress syndrome, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, and irritable bowel syndrome.

28. A method of treating a condition where inhibition of a cGMP-specific PDE is of therapeutic benefit, in a human or a nonhuman animal body, comprising administering to said body a therapeutically effective amount of a compound of claim 1.

29. A method for the curative or prophylactic treatment of male erectile dysfunction or female arousal disorder, comprising administration of an effective dose of a compound of claim 1, and pharmaceutically acceptable salts and solvates thereof, to an animal.

- 122 -

30. Use of a compound of claim 1 for the manufacture of a medicament for the curative or prophylactic treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.